A Dissertation on

NON INVASIVE ASSESSMENT OF FIBROSIS OF LIVER USING FIBROSCAN IN PATIENTS WITH DIABETES MELLITUS

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With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

COIMBATORE

MAY 2019

CERTIFICATE

Certified that this dissertation in "**NON INVASIVE ASSESSMENT OF FIBROSIS OF LIVER USING FIBROSCAN IN PATIENTS WITH DIABETES MELLITUS"** is the bonafide dissertation done by **Dr. R. Nandhini devi** and submitted in partial fulfillment of the requirements for the Degree of **M.D.,General Medicine**, Branch I during the academic year 2016-2019 of **The Tamilnadu Dr. M.G.R. Medical University, Chennai.**

Date: **Guide, Professor &Chief**
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Date: **Professor & Head**
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DECLARATION

I solemnly declare that the dissertation titled **"NON INVASIVE ASSESSMENT OF FIBROSIS OF LIVER USING FIBROSCAN IN PATIENTS WITH DIABETES MELLITUS"** was done by me from JULY 2017 to JUNE 2018 under the guidance and supervision of Professor **Dr.KUMAR NATARAJAN M.D.,**

This dissertation is submitted to **The Tamilnadu Dr.M.G.R. Medical University** towards the partial fulfilment of the requirement for the award of MD Degree in General Medicine(Branch I).

Place: Coimbatore **Dr.R.NANDHINI DEVI**

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Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering His blessings on me and my family**.**

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This is to certify that this dissertation work titled “NON INVASIVE ASSESSMENT OF FIBROSIS OF LIVER USING FIBROSCAN IN PATIENTS WITH DIABETES MELLITUS” of the candidate **DR.R.NANDHINI DEVI** with registration Number **201611310** for the award of M.D in the branch of General Medicine I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 2% (Two percentage) percentage of plagiarism in the dissertation.

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https://www.curejoy.com/content/natural-treatments-for-non-alcoholic-fatty-liver-disease/

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TABLE OF CONTENTS

ABBREVIATIONS

NASH	-	Non Alcoholic Steato Hepatitis
NAFLD	-	Non Alcoholic Fatty Liver Disease
T2DM	-	Type 2 Diabetes Mellitus
HCC	-	Hepatocellular Carcinoma
CT	-	Computerized Tomography
MRI	-	Magnetic Resonance Imaging
AST	-	Aspartate Transaminase
ALT	-	Alanine Transaminase
SGOT	-	Serum Glutamic oxaloacetic transaminase
SGPT	-	Serum Glutamic pyruvate transaminase
ARFI	-	Acoustic Radiation Force Impulse
FBS	-	Fasting Blood Sugar
PPBS	-	Post Prandial Blood Sugar
TNF	-	Tumor Necrosis Factor
BMI	-	Body Mass Index
FFA	-	Free Fatty Acids
VLDL	-	Very Low Density Lipoprotein
IBD	-	Inflammatory Bowel Disease
SAP	-	Serum Alkaline Phosphatase
GGT	-	Gamma Glutamyl Transpeptidase

PPV	-	Positive Predictive Value
NPV	-	Negative Predictive Value
HCV	-	Hepatitis ‘C’ Virus
TGL	-	Triglyceride
HDL	-	High Density Lipoprotein
ANOVA	-	Analysis of Variance

INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) is one the most common liver disorders worldwide. “It is defined as liver fat exceeding 5-10% by weight and exists as a spectrum from steatosis (which is usually stable) to steatohepatitis or non alcoholic steatohepatitis (NASH) (cellular ballooning, necroapoptosis, inflammation and fibrosis) which progress to cirrhosis in 15 – 20% ” [(1).] In the United States NAFLD stands as fourth cause of liver transplantation. Non alcoholic fatty liver disease is closely associated with obesity, insulin resistance and dyslipidemia. The prevalence of NASH is increasing in line with increasing incidence of sedentary life style, obesity and diabetes mellitus. Previously many patients were thought to have cryptogenic cirrhosis show clinical features of NAFLD suggesting that the cause of that cirrhosis could be unrecognized NAFLD. 10-75% of NAFLD patients have T2DM and 21-72% of diabetic patients are found to have NAFLD .[2] NAFLD and diabetes mellitus are highly dependent on genetic background and dietary factors.[(3)] The term NASH or Non alcoholic steatohepatitis was introduced by Ludwig et al., describing the lesion in various degree of severity in patients without significant ethanol exposure .[(3)]

Insulin resistance is very common in NAFLD [(4,5,6)] It can be demonstrated in major insulin targets including adipose tissue (persistent lipolysis), muscle (diminished glucose disposal) and liver (failure to suppress

glucose release). It is estimated that up to 75% of type 2 diabetic have fatty infiltration. [7]

Liver biopsy remains the standard test for confirming the diagnosis, staging fibrosis, grading activity and judging response to treatment. But it has many limitations like patient inconvenience, cost, difficulty in performing in obese patients, sampling error, procedure related complication and even mortality. Liver enzymes and various imaging modalities can be used in the diagnosis of NAFLD. But these will not exactly assess steato hepatitis and fibrosis. These patients are investigated by non invasive modality called fibroscan (Transient elastography). This has become a popular non invasive device to assess the liver hardness or stiffness and quantification of liver steatosis with the Controlled Attenuation Parameter (CAP). Since fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from liver the hardness. The results are expressed in kilopascals (Kpa).

AIM OF THE STUDY

To assess the utility of transient elastography (fibroscan) as a screening tool to detect the presence of fibrosis of liver in the patients with diabetes mellitus with non alcoholic fatty liver disease.

REVIEW OF LITERATURE

HISTORIC PERSPECTIVE:

Ludwig et alin, a Mayo Clinic pathologist, coined the term NASH in non-alcoholics in a paper published in 1980.[3]

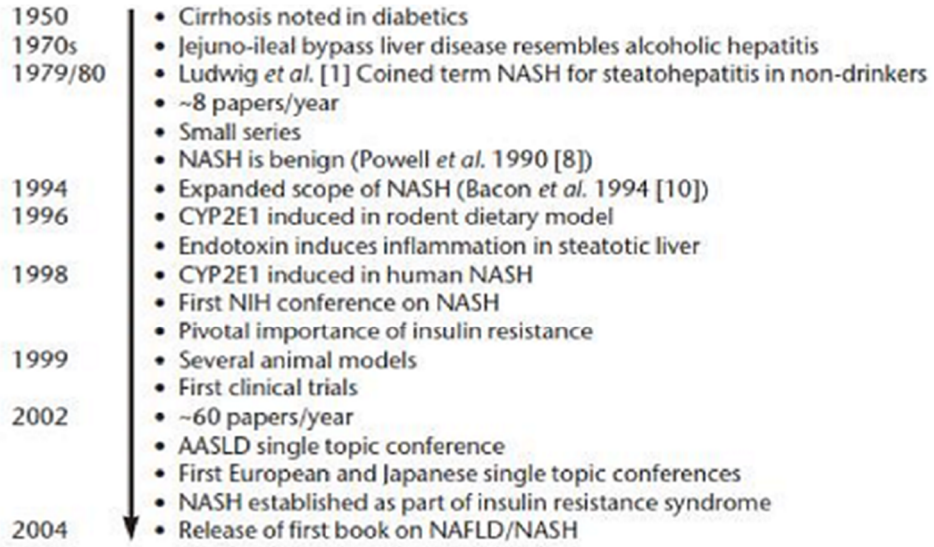
In 1952 Zelman described liver biopsy findings in 19 obese men that included steatosis and varying degrees of inflammation and fibrosis. [8]

Various researches to describe the etiopathogenesis, natural history is stated below;

1. 1950 - cirrhosis noted in diabetes
2. 1970 - jejuno-ileal bypass liver disease resembles alcoholic hepatitis
3. 1979/80- Ludwig et al coined the term NASH for steatohepatitis in non-alcoholics
4. 1994 – expanded scope of NASH (Bacon et al)
5. 1996 – CYP2E1 induced in rodent dietary model Endotoxin induces inflammation in steatotic liver
6. 1998 – CYP2E1 induced in human NASH; Pivotal importance of insulin resistance
7. 1999 – Several animal models; First clinical trial
8. 2002 - ~60 papers/year
    - AASLD single topic conference

- First European and Japanese single topic conferences
- NASH established as part of insulin resistance syndrome

9. 004 – Release of first book on NAFLD/NASH



INCIDENCE AND PREVALENCE:

In general population, 10-24% NAFLD was detected in various countries. The estimation increases from 57.5% [9] to 74% [10,11]

Many meta analysis was done to describe the burden of NAFLD. One meta analysis done in febraury 2016 named “Global epidemiology of non alcoholic fatty liver disease- meta analytic assessment of prevalence, incidence and outcomes.” According to this study, average prevalence of NAFLD in the adult population was 25.24%. The stratification by region as follows:

REGION	N	PREVALENCE(%)
Africa	2	13.48
Asia	14	27.37
Europe	11	23.71
Middle East	3	31.79
North america	13	24.13
South America	2	30.45
overall	45	**25.24**

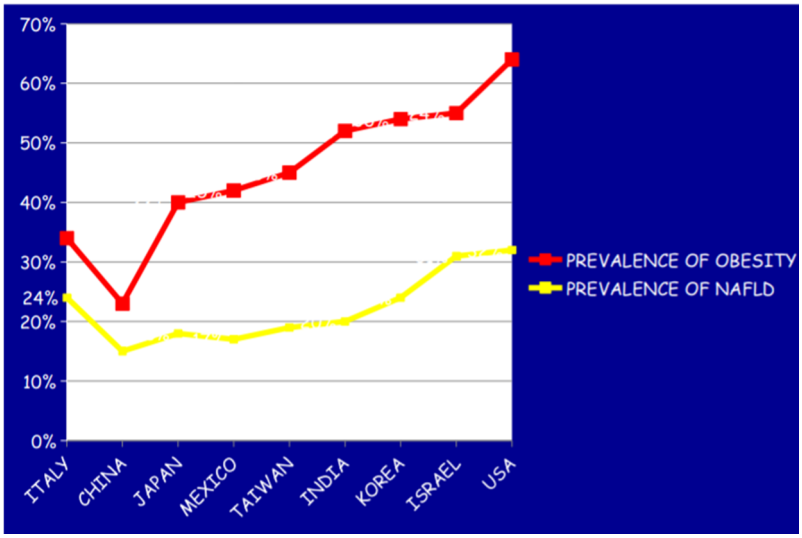
Another study conducted by Lonardo A, Bellantoni S, et al in 2015 showed the following results.

Prevalence of NAFLD by various studies [14]

Author (year)	Study	Diagnostic method	Country	No. of individuals screened	Prevalence of NAFLD (%)	Prevalence of NASH (%)
Browning (2004)	Population-based	MR spectroscopy	USA	2287	31	ND
Bedogni (2005)	Population-based	Ultrasonography	Italy	598	23	ND
Fan (2005)	Population-based	Ultrasonography	China	3175	15	ND
Nomura (1988)	Population-based	Ultrasonography	Japan	2574	14	ND
Clark (2003)	Population-based	Aminotransferases	USA	15 676	5.4	ND
Ruhl (2003)	Population-based	Aminotransferases	USA	5724	2.8	ND
Jimba (2005)	Health evaluation	Ultrasonography	Japan	1950	29	ND
Hamaguchi (2005)	Health evaluation	Ultrasonography	Japan	4401	18	ND
Park (2006)	Health evaluation	Ultrasonography	South Korea	6648	16	ND
Hultcrantz (1986)	Hospital series	Liver biopsy	Sweden	149	39	ND
Lee (1989)	Hospital series	Liver biopsy	USA	543	ND	9
Nonomura (1992)	Hospital series	Liver biopsy	Japan	561	ND	1
Byron (1996)	Hospital series	Liver biopsy	USA	1226	ND	11
Daniel (1999)	Hospital series	Liver biopsy	USA	81	51	32
Berasain (2000)	Hospital series	Liver biopsy	Spain	1075	ND	16
Hilden (1977)	Autopsy series	Liver biopsy	Sweden	503	24	ND
Ground (1982)	Autopsy series	Liver biopsy	USA	423	16	ND
Wanless (1990)	Autopsy series	Liver biopsy	Canada	207	29	6
El-Hassan (1992)	Outpatients	Ultrasonography, CT	Saudi Arabia	1425	10	ND
Lonardo (1997)	Outpatients	Ultrasonography	Italy	363	20	ND
Araujo (1998)	Outpatients	Ultrasonography	Brazil	217	33.5	ND
Omagari (2002)	Outpatients	Ultrasonography	Japan	3432	9	ND
Luyckx (1998)	Bariatric surgery	Liver biopsy	Belgium	528	74	ND
Silverman (1990)	Bariatric surgery	Liver biopsy	USA	100	86	36
Dixon (2001)	Bariatric surgery	Liver biopsy	Australia	105	71	25
Beymer (2003)	Bariatric surgery	Liver biopsy	USA	48	85	33
Spaulding (2003)	Bariatric surgery	Liver biopsy	USA	48	88	56
Mathurin (2006)	Bariatric surgery	Liver biopsy	France	167	ND	14.4
Franzese (1997)[a,b]	Outpatients	Ultrasonography	Italy	72	53	ND
Tominaga (1995)[a]	Health evaluation	Ultrasonography	Japan	810	3	ND
Schwimmer (2006)[a]	Autopsy series	Liver biopsy	USA	742	9.6 (38 among obese)	3

[a]Pediatric series. [b]Obese children. ND, not determined.

Prevalence of obesity and NAFLD as follows:



INDIAN SCENARIO:

There are only limited study on prevalence of NAFLD in India. [12]Chitturi et al in his study described prevalence of fatty liver as 15.8% and 24% in Western India and Eastern India respectively. [13]Mohan et al studied prevalence of NAFLD in type 2 diabetics and found it to be 54.5%. Overall incidence of insulin resistance is high in Asian populations.

LIVER DISEASE IN DIABETES MELLITUS:

2. Liver disease occurring as a consequence of diabetes mellitus.
    - glycogen deposition
    - steatosis and non alcoholic steatohepatitis (NASH)
    - Fibrosis and cirrhosis
    - Biliary disease, cholelithiasis, cholecystitis

- Complications of therapy of diabetes (cholestatic and necroinflamamatory)

2. Abnormalities of glucose homeostasis occurring as a complication of liver disease can be present in

- Hepatitis
- Cirrhosis
- Hepatocellular carcinoma
- Fulminant hepatic failure

3. Liver disease occurring coincidentally with diabetes and abnormalities of glucose homeostasis.

- hemochromatosis
- Glycogen storage disease
- Autoimmune biliary disease

Fatty liver is well recognized complication of type 2 diabetes when compared type 1 diabetes. Type 2 diabetes have 70% correlation to NAFLD regardless of blood glucose control.

Increasing evidence indicates that NAFLD increases the risk of cardiovascular complications, micro and macrovascular complications. The micro and macrovasuclar disease have a great impact on economy of the patient. Both NAFLD and diabetes mellitus increases the risk of developing hepatocellular carcinoma.

Familial clustering of NASH and NAFLD could represent inherited genetic predisposition or common environmental factors such as dietary habits and activity levels.[14,15,16] The finding of impaired skeletal muscle mitochondrial metabolism and insulin resistance in the offspring of patients with diabetes mellitus suggest a genetic risk related to intracellular fat metabolism.[17]

NAFLD CAUSES ARE AS FOLLOWS: [18]

PRIMARY:

1. Obesity
2. Glucose intolerance
3. Type 2 diabetes mellitus
4. Hypertriglyceridemia
5. Low HDL
6. Cholesterol
7. Hypertension

NUTRITIONAL:

1. Protein-calorie malnutrition
2. Rapid weight loss
3. Gastrointestinal bypass surgery
4. Total parenteral nutrition
5. Vitamin B12 deficiency

DRUGS:

1. Glucocorticoids
2. Estrogens
3. Tamoxifen
4. Amiodarone
5. Methotrexate
6. Diltiazem
7. Zidovudine
8. Sodium Valproate
9. Aspirin
10. Tetracycline
11. Cocaine

METABOLIC:

1. Lipodystrophy
2. Hypopituitarism
3. Dysbetalipoproteinemia
4. Weber-Christian disease
5. Wilsons disease
6. Anderson’s disease
7. Mauriac syndrome

TOXINS:

1. Amanita phalloides mushroom
2. Phosphorus poisoning
3. Petrochemicals
4. Bacillus cereus toxin
5. Carbon tetrachloride
6. Vinyl chloride
7. Ethyl bromide

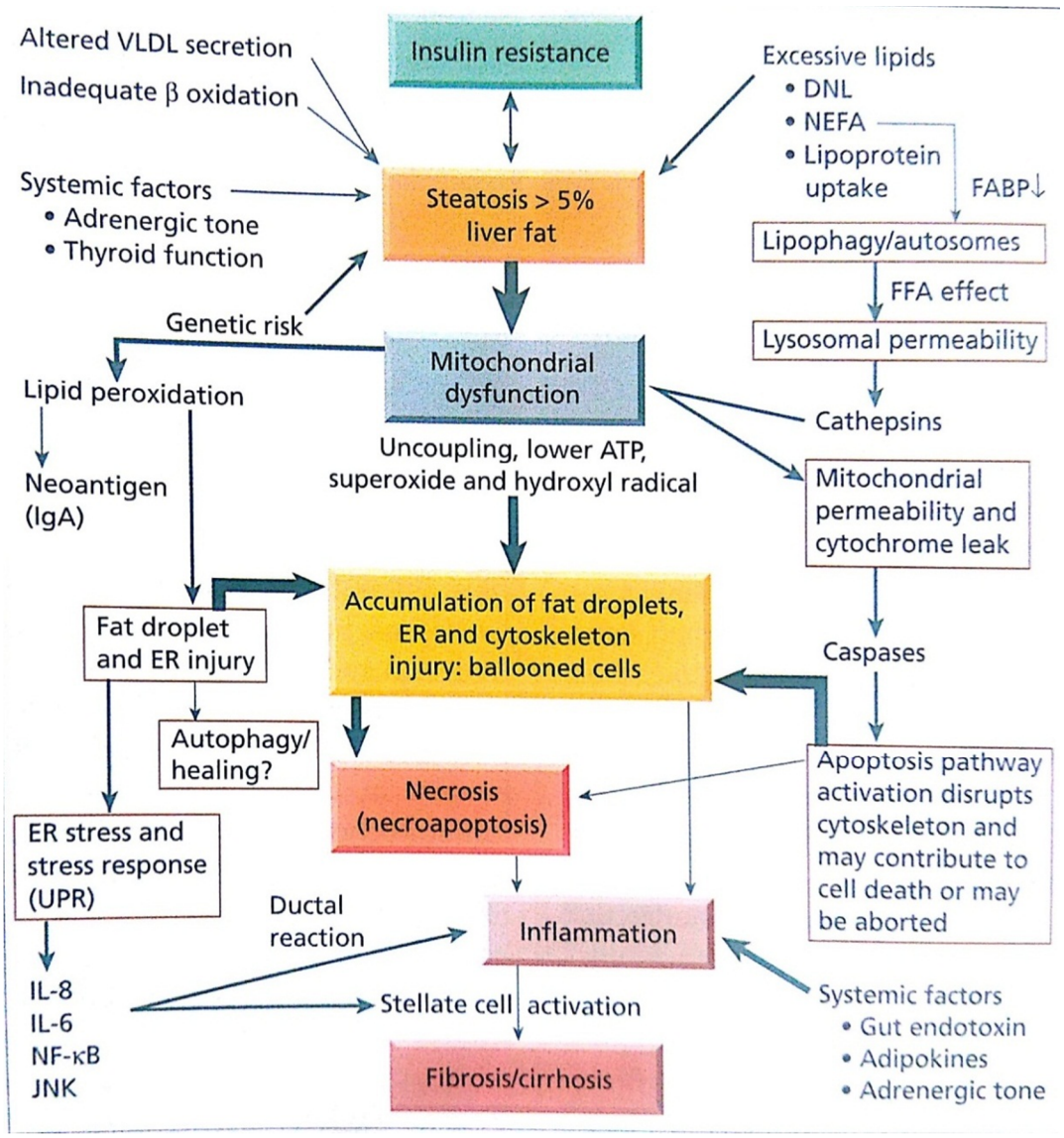
INFECTIONS:

1. Human Immunodeficiency virus
2. Hepatitis C
3. Small bowel diverticulosis with bacterial overgrowth.

PATHOGENESIS OF NAFLD:

Lipid accumulation in the liver results from imbalance between overall calorie intake and utilization which is the characteristic of metabolic syndrome. Hepatic fat results from several possible mechanisms like synthesis of new fatty acids mainly from carbohydrate precursors (de novo lipogenesis), uptake of circulating fatty acids (non esterified fatty acids -NEFA) derived from adipose tissue lipolysis, uptake of diet derived chylomicron remnants, uptake of VLDL derived LDL remnants. Liver fat is disposed of by either oxidation or lipoprotein secretion espectially as VLDL. NAFLD appears to be driven

especially by NEFA uptake , de novo lipogenesis and altered lipid export. Excess Free Fatty Acids (FFA) appears to promote permeabilization of lysosomes and mitochondria with release of cathepsins and cytochrome C, including caspases which activate apoptosis pathway.



Mechanism of Hepatocellular injury in NASH can be encapsulated in the “two hit hypothesis” – accumulation fat followed by oxidative injury.[19]. .

Additionally, a further component called third hit has been added to explain inadequate hepatocyte proliferation. Impaired capacity to regenerate leads to cell death with impaired regeneration of hepatocyte progenitors represent the third hit.

CAUSES OF TRIGLYCERIDES ACCUMULATION IN LIVER:

INCREASED FATTY ACID INFLUX:

1. Obesity
2. Insulin resistance
3. Diet

INCREASED FATTY ACID SYNTHESIS:

1. Hyperinsulinemia
2. Excess carbohydrate food intake
3. Leptin deficiency

INCREASED FATTY ACID OXIDATION

1. Hyperinsulinemia
2. genetic disorders
3. Leptin deficiency
4. Drugs

DECREASED VLDL ASSEMBLY:

1. Genetic disorder
2. Insulin resistance
3. Drugs

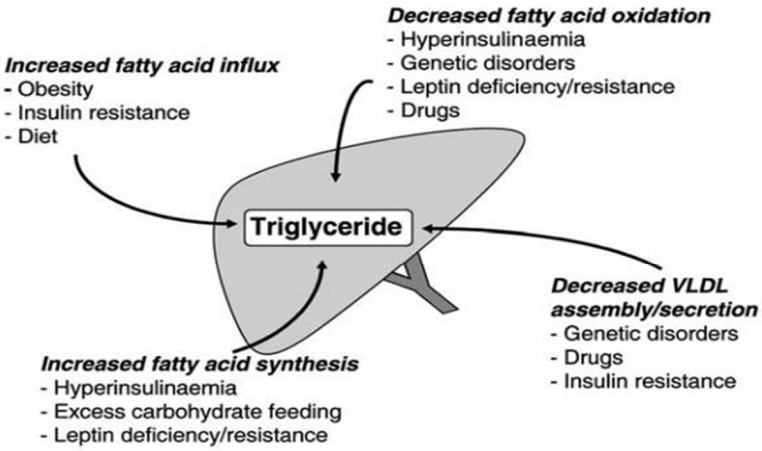


Figure shows Factors involved in triglyceride accumulation in the liver

The process of fibrosis which occurs after the formation of fatty liver involves series of mechanism.

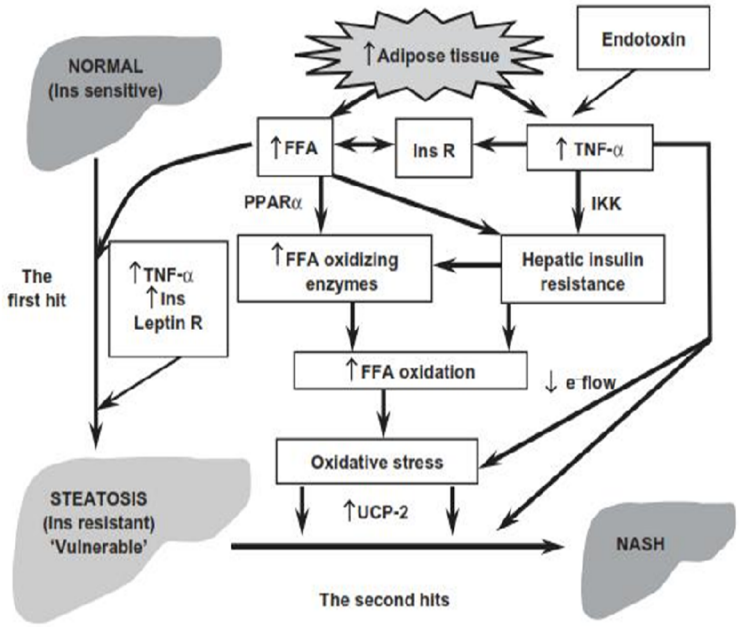
1. Activation of liver kupffer cells

2. Peroxidation of lipids in the mitochondria

3. Oxidative damage to the mitochondria

4. Altered function in the mitochondria

5. Alteration in the cytokine levels



FIBROGENESIS IN NON ALCOHOLIC STEATOHEPATITIS:

Final death may results from combination of necrosis and apoptosis (necroapoptosis).[20] The activation of caspase 3 leads to fragmentation of cytokeratin 18. This leads to the formation of Mallory denk bodies.[21] Accumulation of free fatty acids and impaired function of Endoplasmic reticulum activated Apo B100 leads to accumulation of misfolded proteins within the endoplasmic reticulum.[22] Pro inflammatory cytokines are activated, accumulation of inflammatory infiltrates and activation of collagen producing hepatic stellate cells characterized by transition from a vitamin A rich quiescent cell to a proliferating fibroblast.[23]

Progression of fibrosis may also depend on an altered repair process with impaired hepatocyte replication and increased activity of hepatic progenitor cells leading to a ductular reaction in the portal tracts.

Many systemic factors are also involved in the development of the above process including insulin/glucagon level, the adipose organ, adrenergic system and thyroid axis.

Hepatic and extrahepatic insulin resistance is present in the majority of patients and contributes to the major cause for the pathogenesis of the disease. The following image shows the mechanism of fibrogenesis.

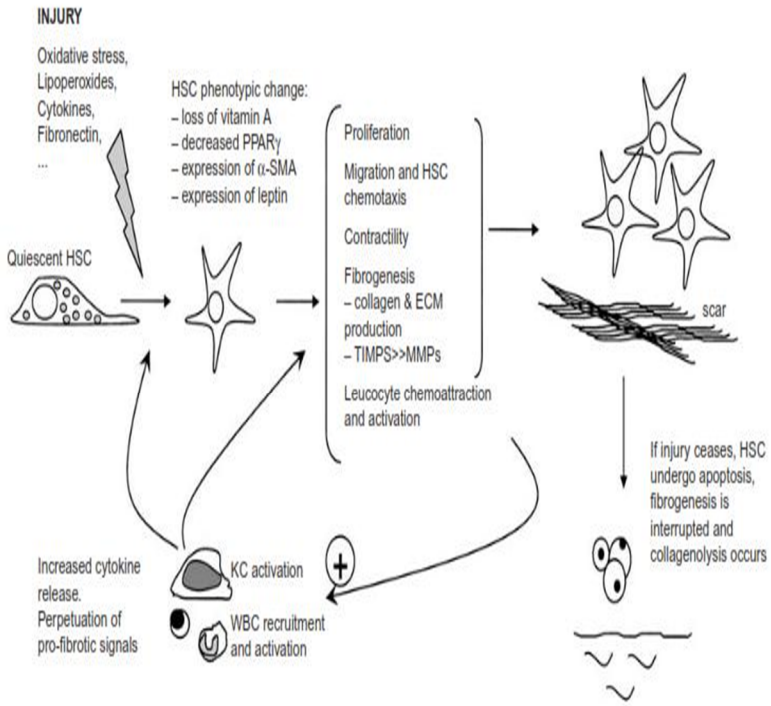
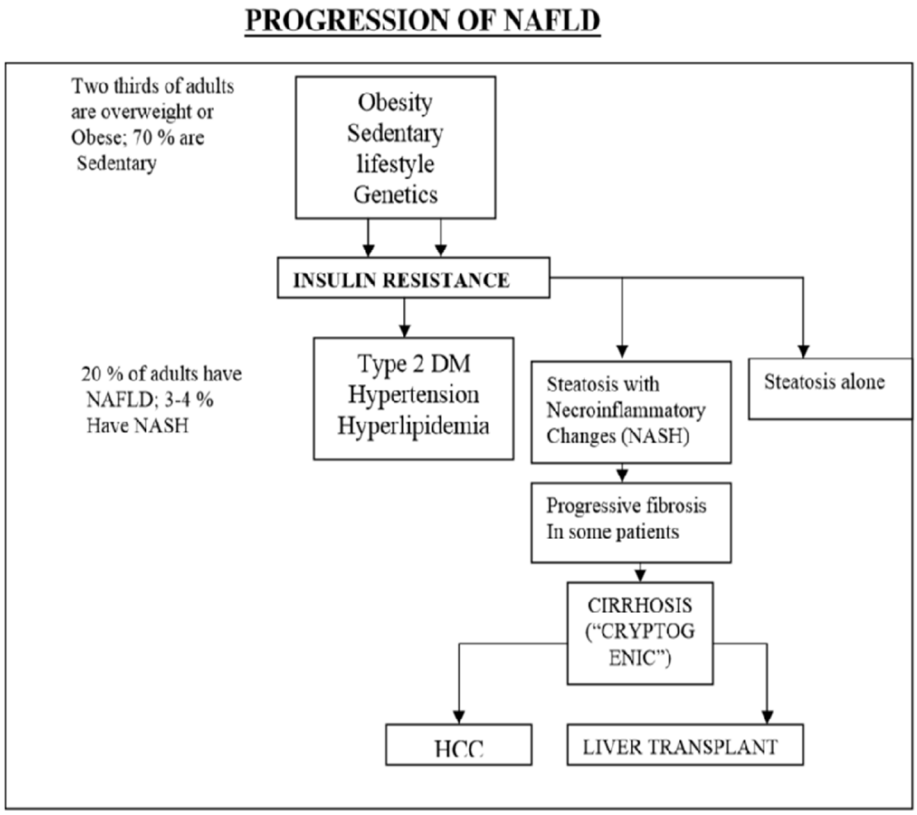


Figure shows the mechanism of fibrogenesis in NASH

The molecular pathogenesis of insulin resistance seems to be multifactorial, and several molecular targets involved in the inhibition of insulin action have been identified. Insulin resistance leads to fat accumulation in hepatocytes by two main mechanisms; **lipolysis and hyperinsulinemia.**

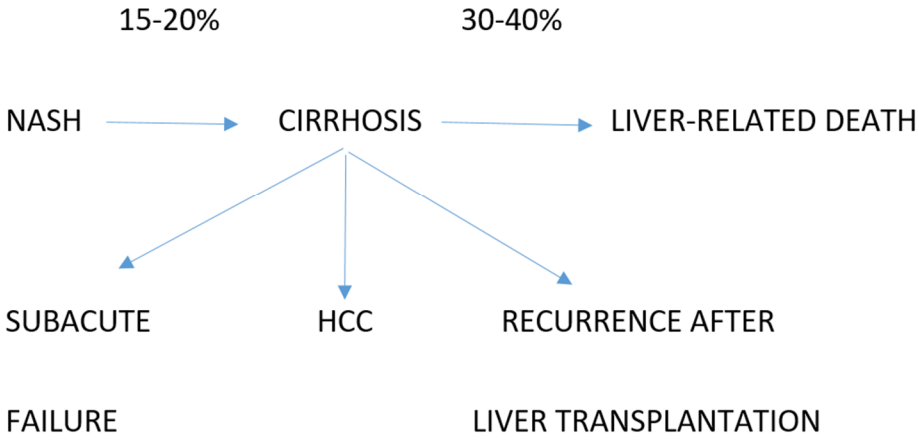
Liver injury worsens with the presence of diabetes in the patients with NAFLD and doubles the prevalence of cirrhosis from 10% to 25%.



NATURAL HISTORY AND PROGNOSIS:

Various factors like obesity, sedentary life styles, genetic factors will lead to insulin resistance. This in turn leads to type 2 diabetes, hypertension and hyperlipidemia. All these factors leads to the formation of NASH or simple steatosis. NASH with severe fibrosis are one of the worst prognosis. [(24)]

In some cases the fibrosis remain static for years, in some it improves, in some patients it gradually worsens and finally leads to cirrhosis and hepatocellular carcinoma.



Many studies showed the prognosis of NASH and the few such studies are listed below.[25]

Table 34.4 Studies on long-term prognosis of nonalcoholic fatty liver disease (NAFLD)

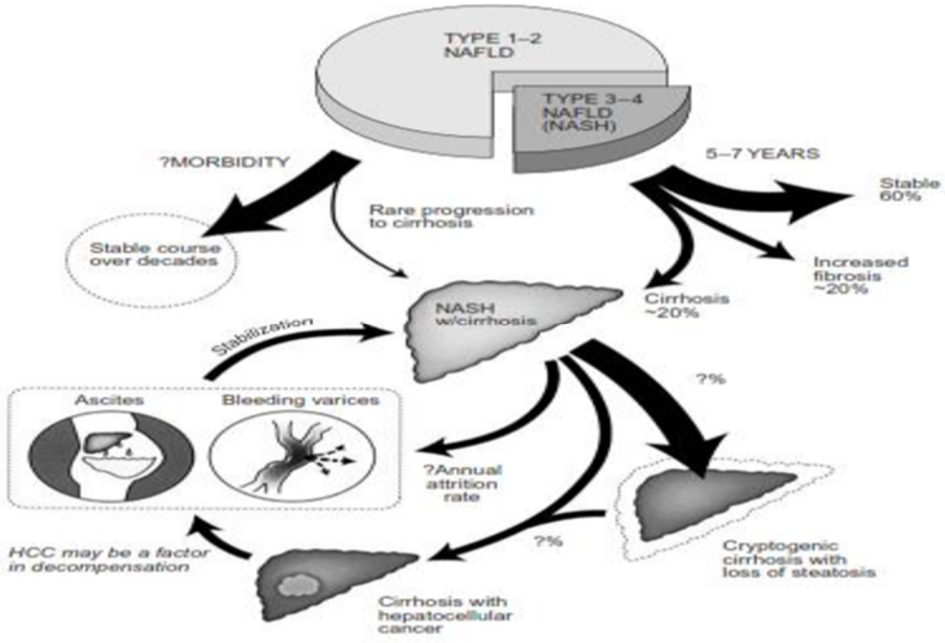
Author (year)	Diagnosis[a]	*n*	Cirrhosis prevalence (%)[b]	No. of liver-related deaths (%)	No. of deaths overall (%)	Average follow-up (years)
Teli (1995)	Bland steatosis	40	0	0	14 (35)	9.6
Dam-Larsen (2004)	Bland steatosis	109	1	1 (0.9)	27 (24.8)	16.7
Matteoni (1999)	NAFLD	98	20	9 (9)	48 (49)	8.3
Adams (2005)	NAFLD	420	5	7 (1.7)	53 (12.6)	7.6
Ekstedt (2006)	NAFLD	129	7.8	2 (1.6)	26 (20.2)	13.7
Lee (1989)	NASH	39	16.3	1 (3)	10 (26)	3.8
Powell (1990)	NASH	42	7	1 (2)	2 (5)	4.5
Evans (2002)	NASH	26	4	0	4 (15)	8.7
Hui (2004)	Cirrhotic-stage NASH	23	100	5 (21)	6 (26)	5.0
Hashimoto (2005)	NASH with septal fibrosis or cirrhosis	89	48	6 (6.7)	8 (9)	3.7
Sanyal (2006)	Cirrhotic-stage NASH	152	100	22 (14.5)	29 (19.1)	10

[a]NAFLD denotes the inclusion of both patients with simple steatosis and patients with nonalcoholic steatohepatitis (NASH).
[b]Cirrhosis prevalence includes all patients diagnosed with cirrhosis at both baseline and during follow-up.

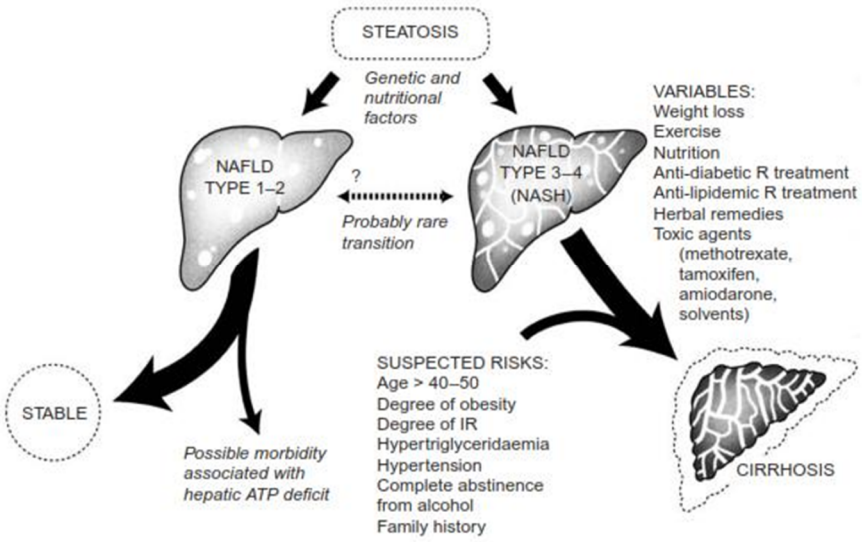
CLASSIFICATION OF NAFLD:[26]

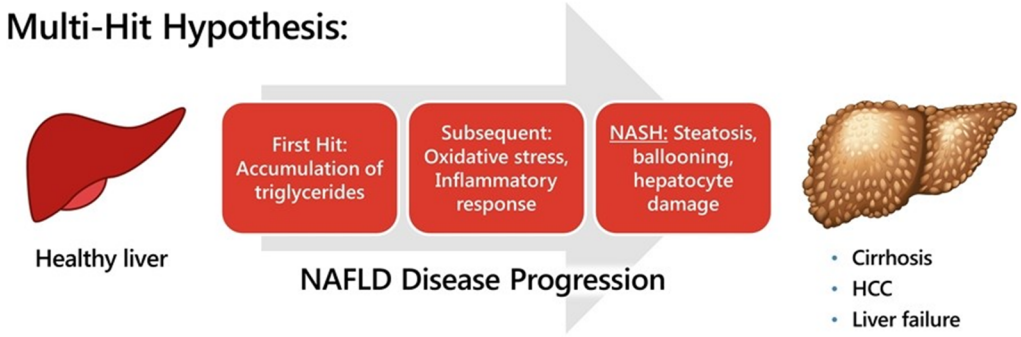
CATEGORY	PATHOLOGY	CLINICOPATHOLOGICAL CORRECTION
TYPE 1	Simple steatosis	Known to be non-progressive
TYPE 2	Steatosis plus lobular inflammation	Probably benign (not regarded as NASH)
TYPE 3	Steatosis, lobular inflammationand ballooning degeneration	NASH without fibrosis-may progress to cirrhosis
TYPE 4	Steatosis, ballooning degeneration and Mallory bodies, and/or fibrosis	NASH with fibrosis-may progress to cirrhosis and liver failure

NAFLD OUTCOMES:



FACTORS INVOLVED IN PATHOGENESIS:





CLINICAL FEATURES :

Most of the patients with NAFLD are usually asymptomatic[27]. Some complaints of discomfort in the right hypochondrium [28] The majority of patients are overweight with BMI of >25 kg/m2, and one-third have metabolic syndrome.[29,30,31] Hepatomegaly present in some cases but signs of chronic liver disease is uncommon.

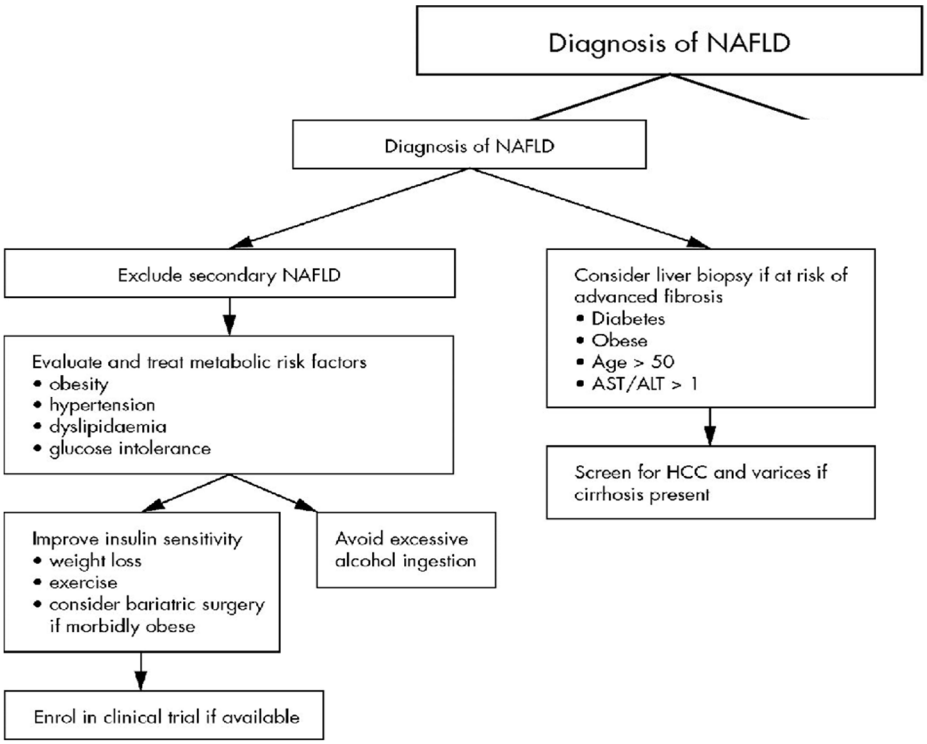
Hepatomegaly is the only physical finding in most patients. Acanthosis nigricans may be seen in children with nonalcoholic fatty liver disease.[32]

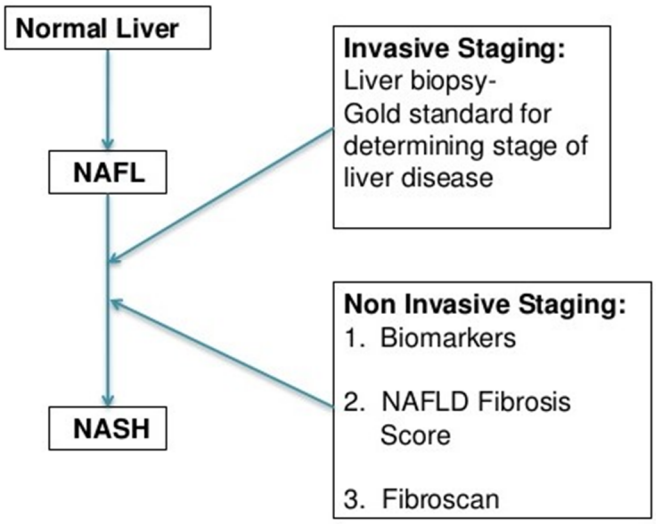
Findings of chronic liver disease and diminished number of platelets suggest that advanced disease with cirrhosis is present. A high proportion of patients with cryptogenic cirrhosis share many of the clinical and demographic features of patients with nonalcoholic fatty liver disease, [33] suggesting that their cryptogenic cirrhosis is unrecognized nonalcoholic fatty liver disease.

Common symptoms and signs of 400 subjects with NAFLD (Data from the NAFLD clinic at Virginia Commonwealth University, previously unpublished data).[38]

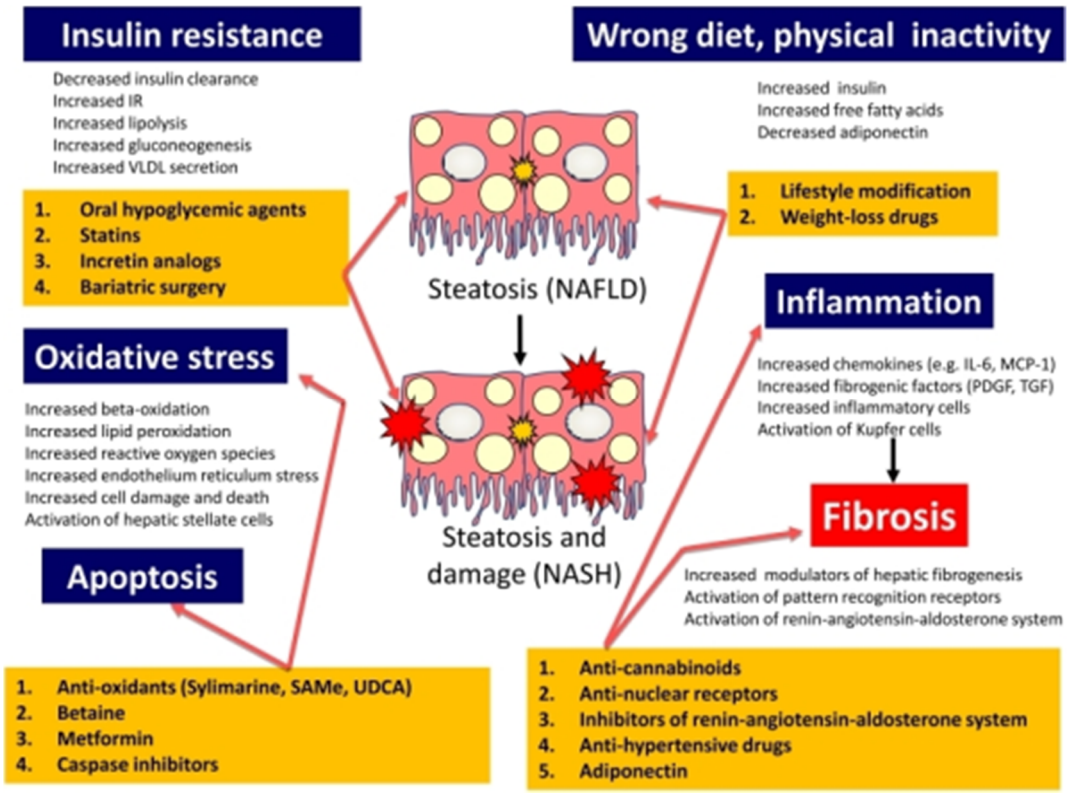
Symptoms and signs	NAFLD (N=75) %	NASH (N=325) %
Asymptomatic	60	55
Fatigue	30	45
Pruritis	2	4
Rt. upper quadrant discomfort	30	32
Edema	4	5
hepatomegaly	22	28
Stigmata of chronic liver disease	8	10
Diabetes	45	50
Hypertension	60	65
Obesity	65	60

The above table shows that majority are asymptomatic and most of the patients are obese.





TREATMENT OF NAFLD:



1. Treatment of associated disorders like gradual weight loss, control diabetes mellitus, control dyslipidemia.
2. Pharmacological approach to treat insulin resistance, dyslipidemia, giving anti oxidants.
3. Liver transplantation is the definitive treatment in case of severe fibrosis or cirrhosis.

LABORATORY ABNORMALITIES:

In patients with NAFLD, aspartate aminotransferases and alanine aminotransferases are mild to moderately elevated. This is most common and sometimes only laboratory abnormality found. The ratio of aspartate aminotransferase to alanine aminotransferase is usually less than 1, but may increases as fibrosis advances, and so accuracy in diagnosing patients with cirrhotic nonalcoholic fatty liver disease becomes less.[34] Serum alkaline phosphatase, gamma glutamyltransferase, or both are above the normal range in many patients, rise is not much when compared to alcoholic hepatitis. An ALT or AST value >300 IU/L should raise the suspicion of alternate cause.[35] The degree of abnormality is usually moderate and does not exceed 2-3 times the upper limit of normal values. But none of these tests are sensitive or specific enough to establish a diagnosis of NAFLD with great accuracy. Isolated elevation of SAP can also be seen.[36]

Other abnormalities including hypoalbuminemia, a prolonged prolonged prothrombin time, and hyperbilirubinemias, may be found in patients with cirrhotic stage nonalcoholic fatty liver disease.

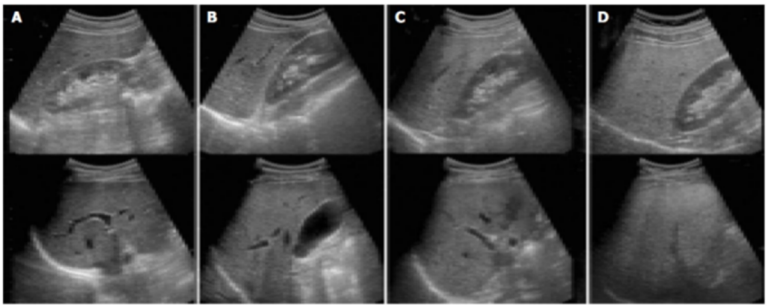
CALCULATION OF INSULIN RESISTANCE:

1. HOMA (homeostasis model assessment) >1.8 – 2
2. QUICKI (quantitative insulin sensitivity check index) <0.35
3. Rough estimate- Fasting insulin x fasting glucose- >700

LIVER IMAGING:

Imaging of liver plays an important role in the clinical diagnosis of NAFLD and also for epidemiological purposes. But the conventional techniques are not accurate in grading the NASH and are insensitive to hepatic fat that is less than 20% by weight.[37] Cross-sectional imaging is used to assess fat distribution (visceral versus peripheral fat) by determining the fat area at specific levels such as L4-5.[38] .

USG abdomen is used as a first line imaging modality in patients suspected of liver disorders. It shows good correlation with the histological finding of fatty liver. In USG, the evidence of steatosis is seen as increased echogenicity (bright scan) .



ABOVE FIGURE SHOWS USG GRADING OF STEATOSIS:

A :NORMAL

B: Grade 1(mild) – Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.

C:Grade 2(moderate) - Increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm.

D:Grade 3(severe) - Increased hepatic echogenicity with imperceptible periportal echogenicity, with obscuration of diaphragm.

Doppler perfusion index is defined as the ratio of arterial blood flow to total blood flow in liver. Liver hemodynamics are altered in case of NAFLD.[39]

Unenhanced computed tomography (CT) relies on attenuation differences between the liver and spleen.[40] Sensitivity and specificity for fatty liver were 84% and 99% respectively, for a spleen minus liver value of > 10 Hounsfield units in one study.[41]

Figure showing CT SCAN image of fatty liver with low attenuation of liver when compared to spleen

Magnetic resonance proton spectroscopy is the most accurate means of quantifying steatosis.

Chemical shift gradient – echo imaging with in phase and opposed-phase acquitions are used in MRI. MRI on T1 weighted images shows intracellular fatty infilteration and loss of signal on opposed phase chemical shift image. MR spectroscopy is capable of measuring accurately adenosine

triphosphate (ATP), lipid peroxidation, and the phospholipid content of liver.[42]

LIVER BIOPSY:

Liver biopsy is the only way to confirm the presence or absence of NASH in a person with features of NAFLD, and histology remains the only criterion for fibrotic severity.[43] The presence of warning signs of cirrhosis is a stronger indication for liver biopsy in order to document with higher certainity the cause of liver disease- occasionally , an unsuspected alternative cause of liver disease may be present.[43]

LIVER BIOPSY – HISTOLOGY

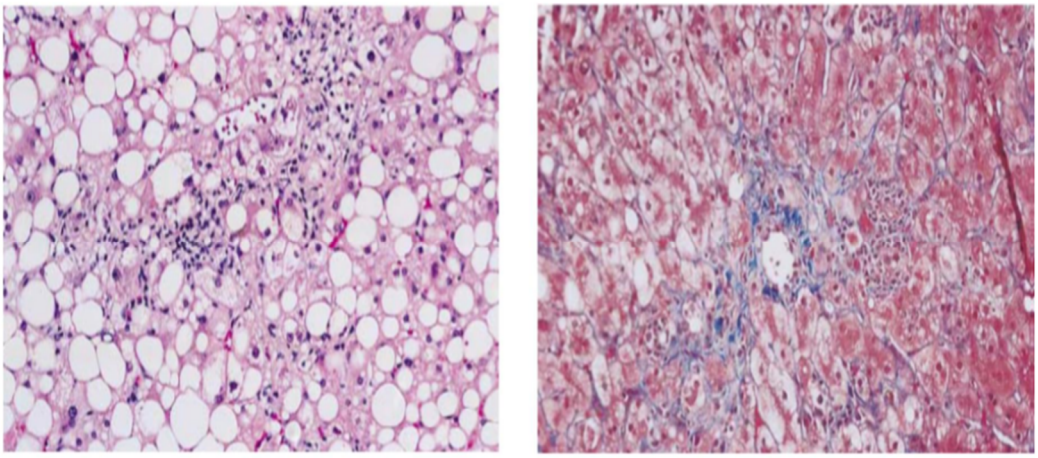


FIGURE A: Macro vesicular steatosis with inflammatory infilterate, hepatocyte ballooning and Mallory's hyaline.

FIGURE B: perivenular, pericellular and perisinusoidal fibrosis shown by Masson's trichrome stainings in zone 3 ("CHICKEN WIRE" fibrosis).

GRADING OF STEATOSIS: [44]

GRADE 1	FAT DROPLETS IN <33% HEPATOCYTES.
GRADE 2	FAT DROPLETS IN 33-66% HEPATOCYTES.
GRADE 3	FAT DROPLETS IN >66% HEPATOCYTES.

GRADING OF NECROINFLAMMATION: (AFTER BRUNT) [44]

Grade	**Ballooning**	**Lobular inflammation**	**Portal inflammation**
GRADE 1 MILD	Occasional, zone 3 hepatocytes	Polymorphs and mononuclear cells, mild and scattered	None or mild
GRADE 2 MODERATE	Obvious, present in zone 3	Polymorphs associated with ballooned hepatocytes+/- mild mononuclear cells	None, mild or moderate
GRADE 3 SEVERE	Marked, predominantly zone 3	Polymorphs concentrated in areas of ballooning; inflammation more than in grade 2	Mild or morderate, not marked.

STAGING OF FIBROSIS:

STAGE 1	Zone 3 pericellular fibrosis (focal or extensive)
STAGE 2	Zone 3 pericellular fibrosis (focal or extensive) plus portal fibrosis (focal or extensive)
STAGE 3	Bridging fibrosis (focal or extensive)
STAGE 4	Cirrhosis, +/- foci of residual pericellular fibrosis.

NON INVASIVE ASSESSMENT OF NASH AND ADVANCED FIBROSIS:

1. The NAFLD Fibrosis score
2. Enhanced Liver Fibrosis Panel
3. Transient elastography
4. Circulating levels of cytokeratin 18.

PREDICTORS OF MORE SEVERE HISTOLOGY IN NASH:

1. age >40-50 yeays
2. degree of obesity
3. hypertension
4. overt diabetes mellitus
5. hypertriglyceridemia
6. elevated ALT
7. elevated AST
8. AST:ALT ratio >1

9. elevated serum IgA level
10. family history of NASH or cryptogenic cirrhosis

LIVER STIFFNESS (LS) MEASUREMENT:

Liver stiffness named as modulus of elasticity which is based on the principle of Hooks law which is expressed as kilopascals (Kpa). LS is based on following characteristics:

1. extracellular matrix,
2. constraints or pressure applied,
3. internal pressure inside the liver,
4. viscous effects.

TRANSIENT ELASTOGRAPHY:

It is a non invasive ultrasound technique used to assess the fibrosis of liver. This has become a popular non invasive device to assess the liver hardness or stiffness and quantification of liver steatosis with the Controlled Attenuation Parameter (CAP). This fibroscans use “Vibration Controlled Transient Elastography” (VCTE) technology to generate precise quantitative measurements of key liver parameters. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called as shear wave) generated on the skin. Shear wave velocity is determined by measuring the time taken by the vibration wave to travel to a particular depth inside the liver. Since fibrous tissue is harder than normal liver, the degree of hepatic fibrosis

can be inferred from liver the hardness. The results are expressed in kilopascals (kPa).

The test is performed with the patient lying supine, an ultrasound-like probe is placed on the skin over the liver area, typically in the right mid-axillary line. The patient will feel a ‘flick’ each time a vibration wave is generated by the probe. Approximately it takes around 10 minutes to perform this test.

Fibroscan is especially used to assess the degree of liver scarring i.e., stage of liver disease. This is useful in patients with chronic liver disease, including chronic hepatitis C, chronic hepatitis B, alcoholic liver disease, fatty liver. This measurement is used to

- Estimate the existing degree of liver damage.
- Monitor disease progression or regression by serial measurements.
- Guide prognosis and further management.

Since this transient elastography doesnot measure he fibrosis directly some amount of over estimation i.e., false positive results may occur. It may occur in case of

- Acute hepatitis
- Cholestasis
- Hepatocellular carcinoma
- Congestion of liver

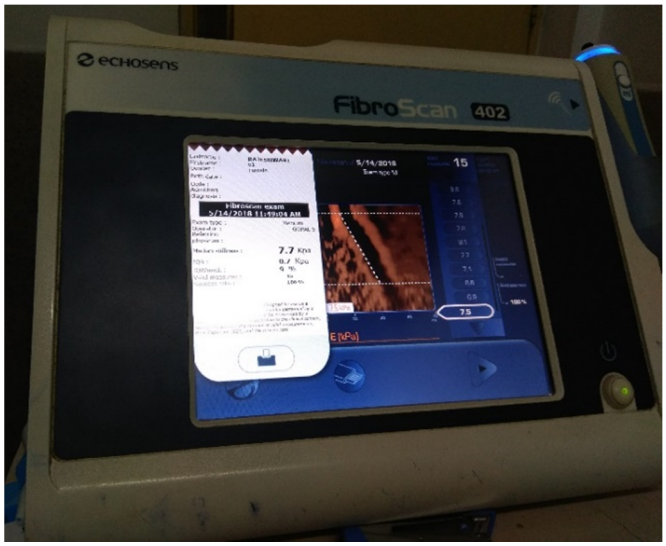
Unreliable readings are more frequently seen in the following patients.

- Obesity (BMI > 30-35 kg/m2)
- Older age
- Presence of ascites
- Metabolic syndrome (increased waist circumference)

Conventional ultrasound is used to assess the structural integrity of liver but fibroscan is superior to ultrasound in detecting the liver scarring and therefore may be used to determine cirrhosis is present at initial assessment and its progression in the follow-up. Fibroscan results range from 2.5 kPa to 75 kPa. Normal people without liver disease can have liver scarring measurement of < 6 kPa.

ADVANTAGES:

1. Rapid procedure
2. Painless
3. Results are immediately available
4. No inter and intra observer variability
5. Easy to perform in out patient clinic



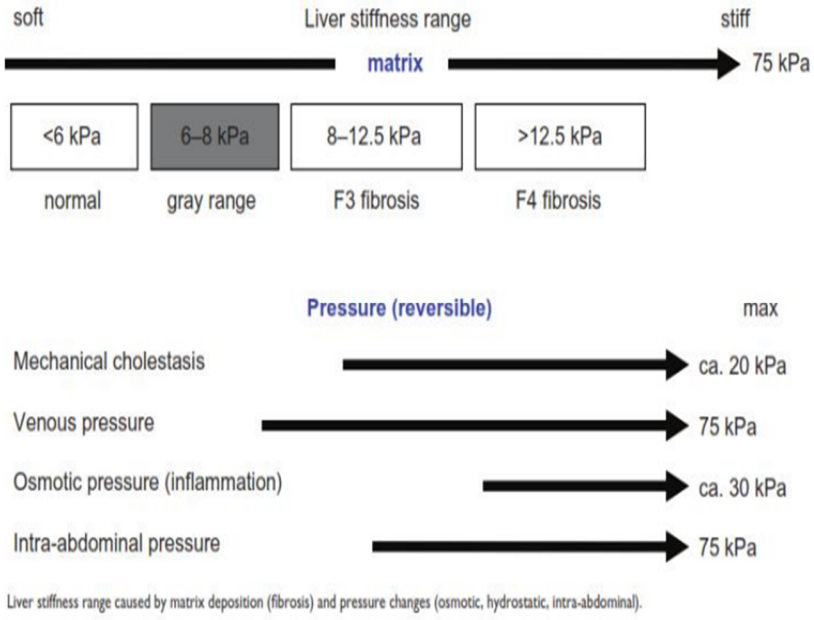
FIBROSCAN MONITOR

Liver stiffness assessment in identifying advanced fibrosis and cirrhosis using fibroscan outscores all noninvasive methods.

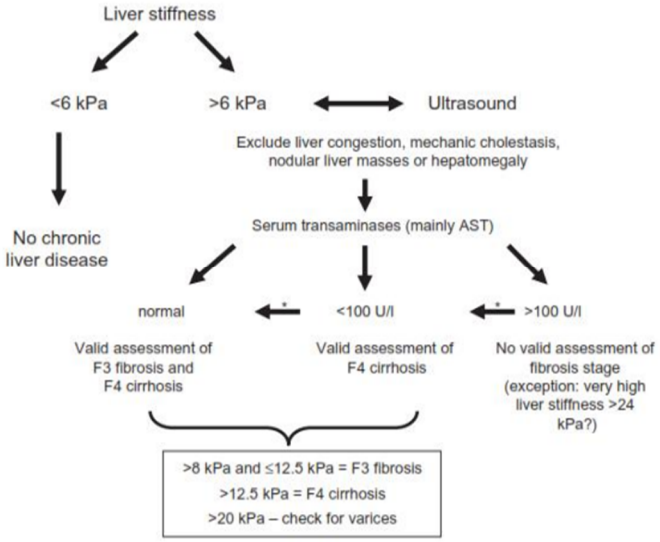
LS <6kPa - normal

LS between 8-12.5 - cut-off values to detect F3 and F4 fibrosis

LS >20 kPa - highly correlates with development of portal pressure, Esophageal varices



Liver stiffness range caused by matrix deposition (fibrosis) and pressure changes (osmotic, hydrostatic, intra-abdominal).



ROLE OF SERUM FERRITIN:

Serum ferritin is elevated in hepatic inflammation. Values are elevated in ~60% of patients with NASH, but do not usually indicate an increase in hepatic iron stores because serum tranferin saturation or stainable iron in liver biopsy is not increased.

METHODS AND MATERIALS

SOURCE OF THE STUDY:

Data consists of primary data collected directly from the cases admitted in medical ward in Coimbatore Medical College and Hospital with Diabetes Mellitus.

DESIGN OF THE STUDY:

It is a Prospective study.

PERIOD OF STUDY:

One year; July 2017 to June 2018

METHODOLOGY:

This is a prospective study of 60 cases of diabetes mellitus with fatty liver admitted in the medical ward of Coimbatore Medical College and Hospital. Diabetes was confirmed with Fasting and post prandial blood sugar and HbA1c are screened for fatty liver with Ultrasound. Detailed history regarding duration of diabetes, history of drug intake , any other past illnesses were taken.Those patients with fatty liver are taken in to study and screened for fibrosis of liver using non invasive method – Fibroscan. Complete Blood count, Liver function test, Lipid profile, viral markers are done to all the patients.

INCLUSION CRITERIA:

1. All patients above the age of 18 years diagnosed as diabetic (with WHO criteria).
2. USG abdomen showing fatty liver.

EXCLUSION CRITERIA:

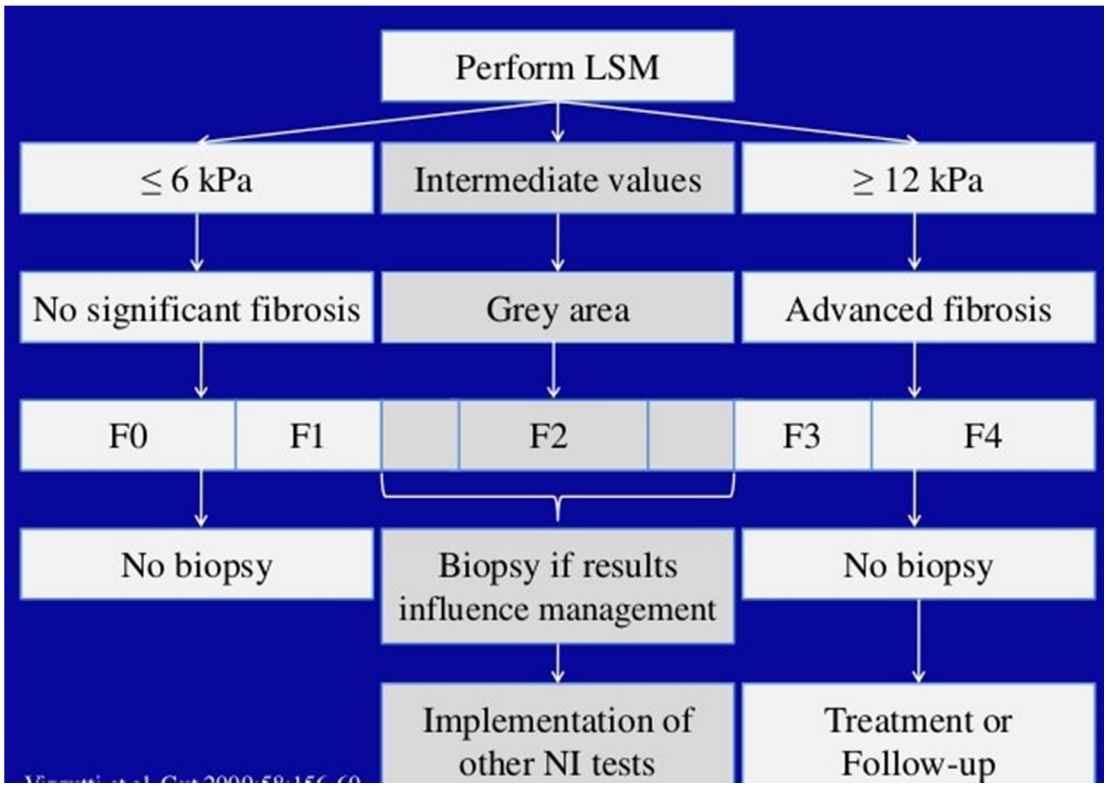
1. Patients with chronic liver disease of any other etiology other than NAFLD.
2. Patients with history of hepatotoxic drug intake.
3. History of alcohol consumption.
4. Pregnancy.
5. Dyslipidemia.
6. Consent not given.

USG GRADING OF FATTY LIVER:

Grade 1 (mild) – Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.

Grade 2 (moderate) - Increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm.

Grade 3 (severe) - Increased hepatic echogenicity with imperceptible periportal echogenicity, with obscuration of diaphragm.


Perform LSM
≤ 6 kPa
Intermediate values
≥ 12 kPa
No significant fibrosis
Grey area
Advanced fibrosis
F0
F1
F2
F3
F4
No biopsy
Biopsy if results influence management
No biopsy
Implementation of other NI tests
Treatment or Follow-up

RESULTS

TABLE 1: GRADING OF NAFLD BY ULTRASOUND

USG GRADING	NO OF PATIENTS	PERCENTAGE
GRADE I	20	33%
GRADE II	26	43%
GRADE III	14	24%

Total number of patients in this study is 60. Out of 60 patients 33% has Grade I fatty liver, 43% has Grade II fatty liver, 24% has grade III fatty liver.

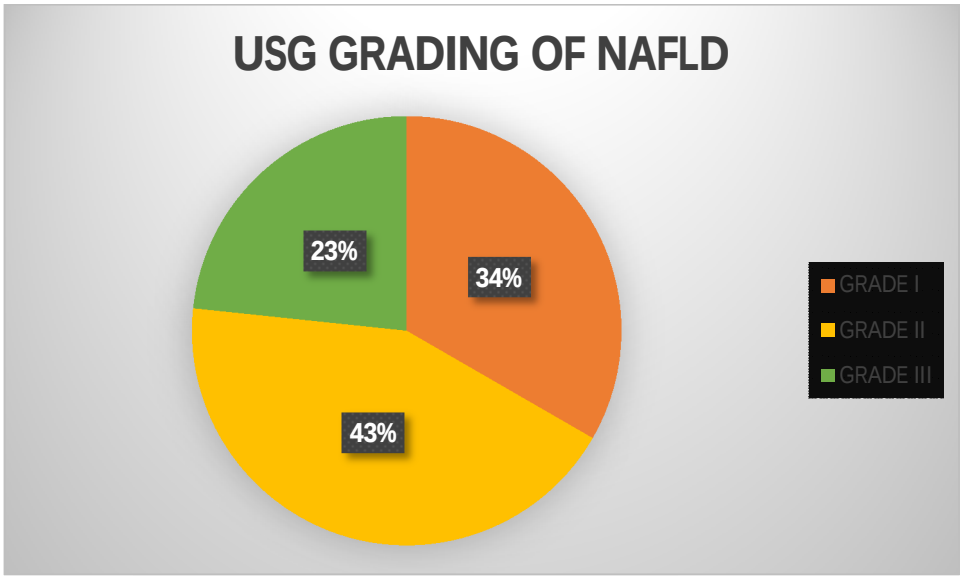


TABLE 2: AGE DISTRIBUTION

AGE IN YEARS	NO OF PATIENTS	PERCENTAGE
< 50	12	20%
51-60	36	60%
> 60	12	20%

In this study majority are in the age group of 51 – 60 years.

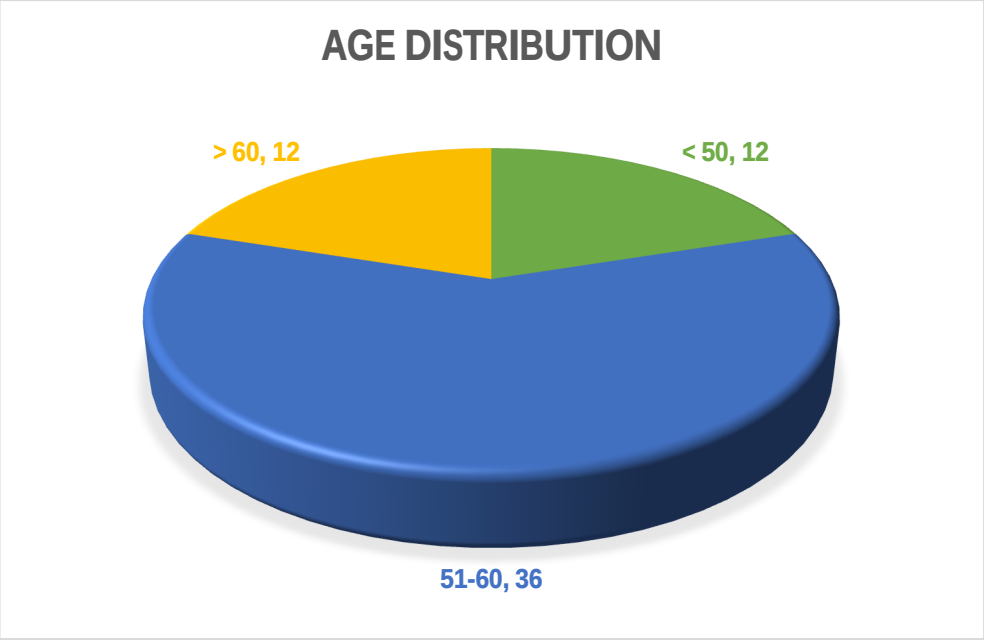


TABLE 3: AGE DISTRIBUTION AMONG NAFLD

USG GRADING	AGE IN YEARS	
	MEAN	SD
GRADE I	54.2	5.97
GRADE II	57.65	6.01
GRADE III	56.71	4.21
ANOVA		
P VALUE - 0.123		
NON SIGNIFICANT		

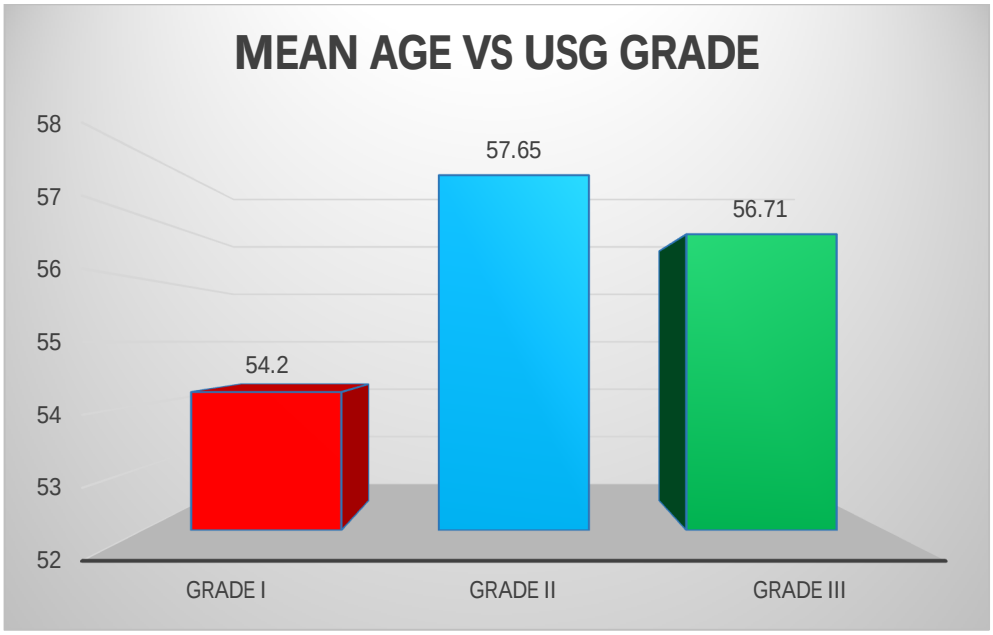


TABLE 4: SEX DISTRIBUTION

SEX	NO OF PATIENTS	PERCENTAGE
MALE	26	43%
FEMALE	34	57%

In this study majority are females. Out of 60 patients 34 (57%) are females .

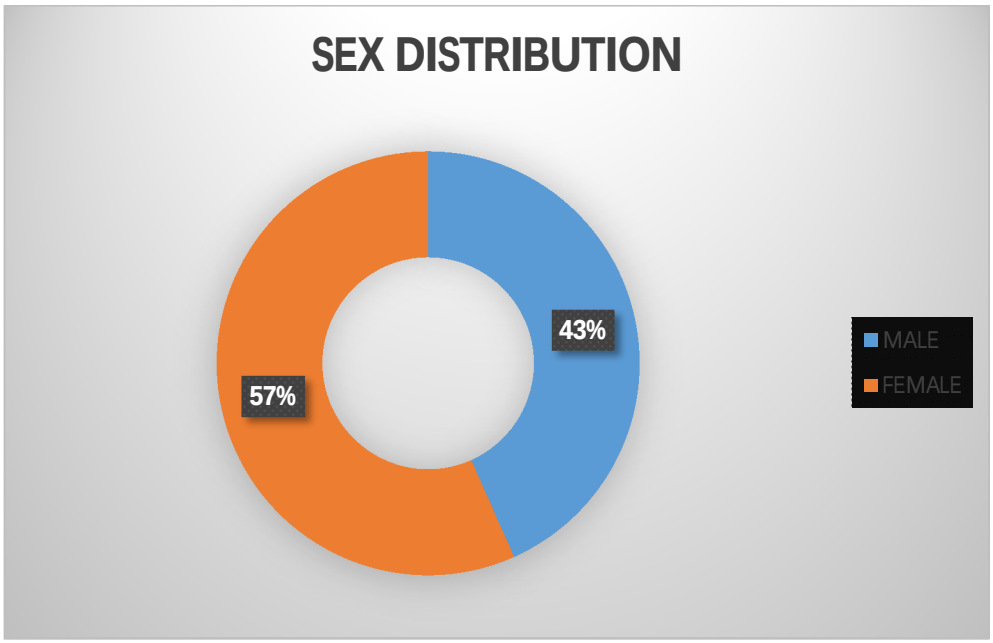


TABLE 5: DISTRIBUTION OF SEX AMONG NAFLD

USG GRADING	SEX	
	MALE	FEMALE
GRADE I	8	12
GRADE II	12	14
GRADE III	6	8
KRUSKAL WALLIS TEST		
P VALUE - 0.916		
NON SIGNIFICANT		

Females are majority in this study. Females are 12, 14, 8 in number who has grade I, grade II, grade III fatty liver respectively

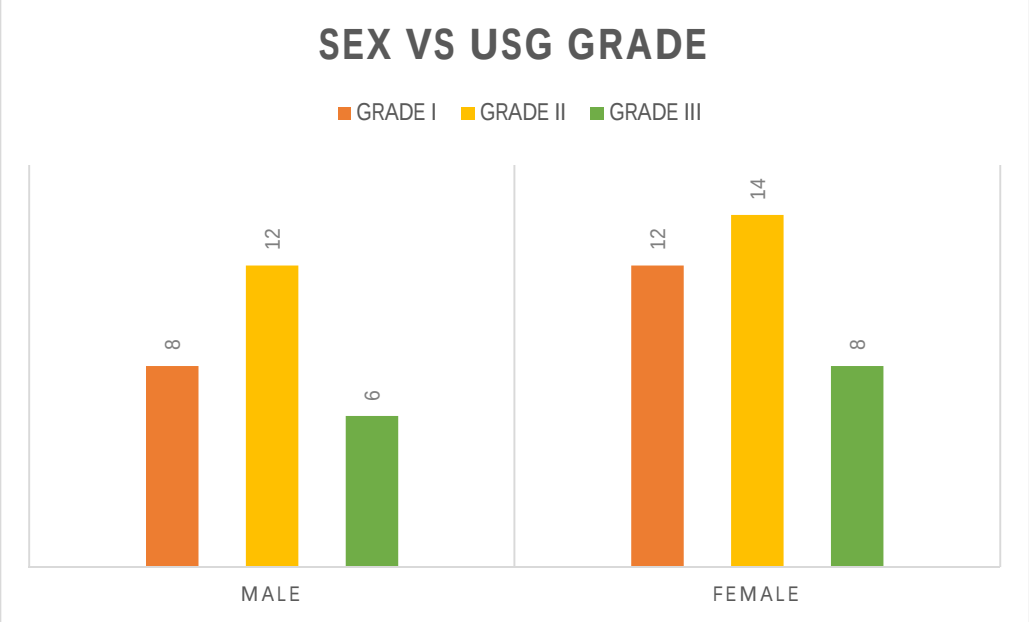
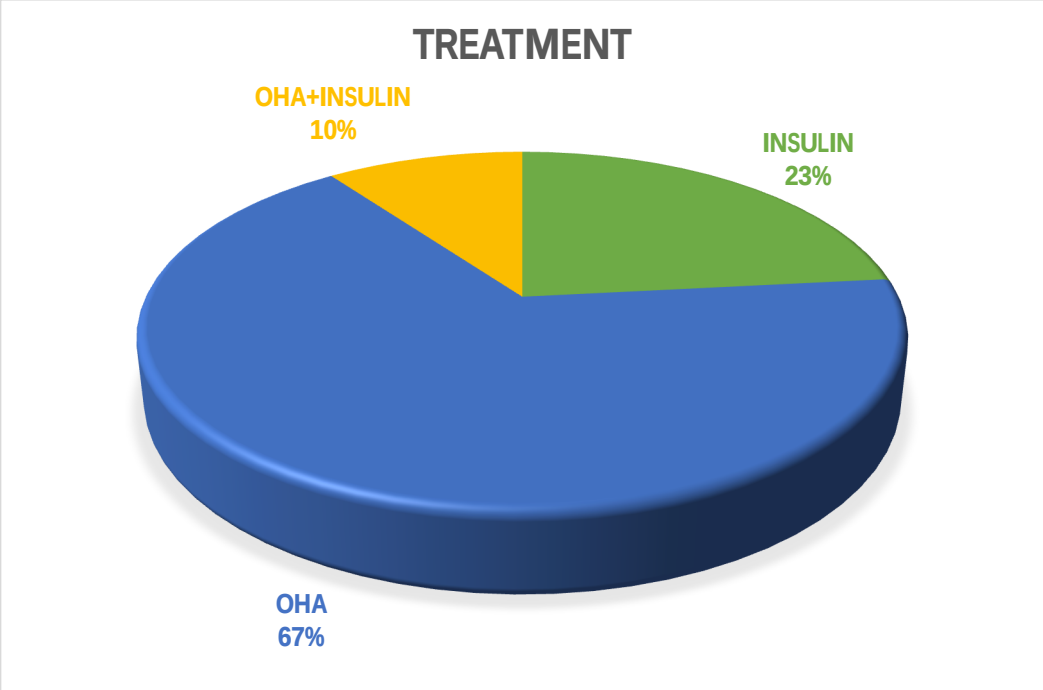


TABLE 6: TREATMENT DETAILS OF THE PATIENTS

TREATMENT	NO OF PATIENTS	PERCENTAGE
INSULIN	14	23%
OHA	40	67%
OHA+INSULIN	6	10%



Out of 60 patients, 14 patients who was in insulin 5, 6, 3 patient has grade I, grade II, grade III fatty liver. 40 patients was on oral hypoglycemic drugs of which 14, 18, 8 patients has grade I, grade II, grade III fatty liver. 6 patients was on combined insulin and oral drugs.

TABLE 7: COMPARISON OF TREATMENT OF PATIENT WITH NAFLD

USG GRADING	TREATMENT		
	INSULIN	OHA	OHA+INSULIN
GRADE I	5	14	1
GRADE II	6	18	2
GRADE III	3	8	3
KRUSKAL WALLIS TEST			
P VALUE - 0.598			
NON SIGNIFICANT			

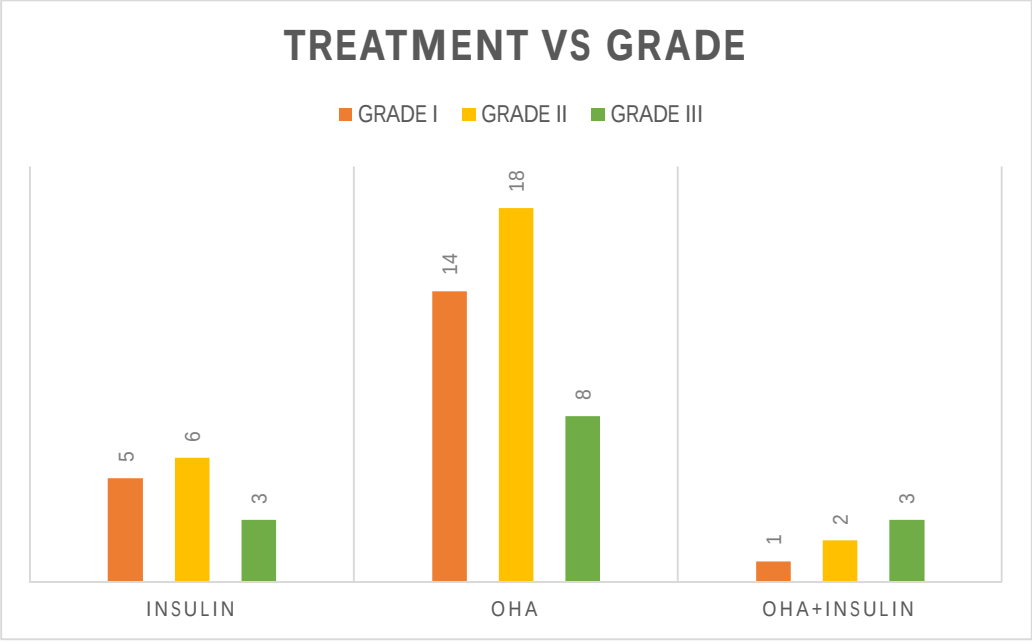


TABLE 8: BODY MASS INDEX OF THE PATIENTS.

BMI (Kg/m^2)	NO OF PATIENTS	PERCENTAGE
MORE THAN 25	28	47%
LESS THAN 25	32	53%

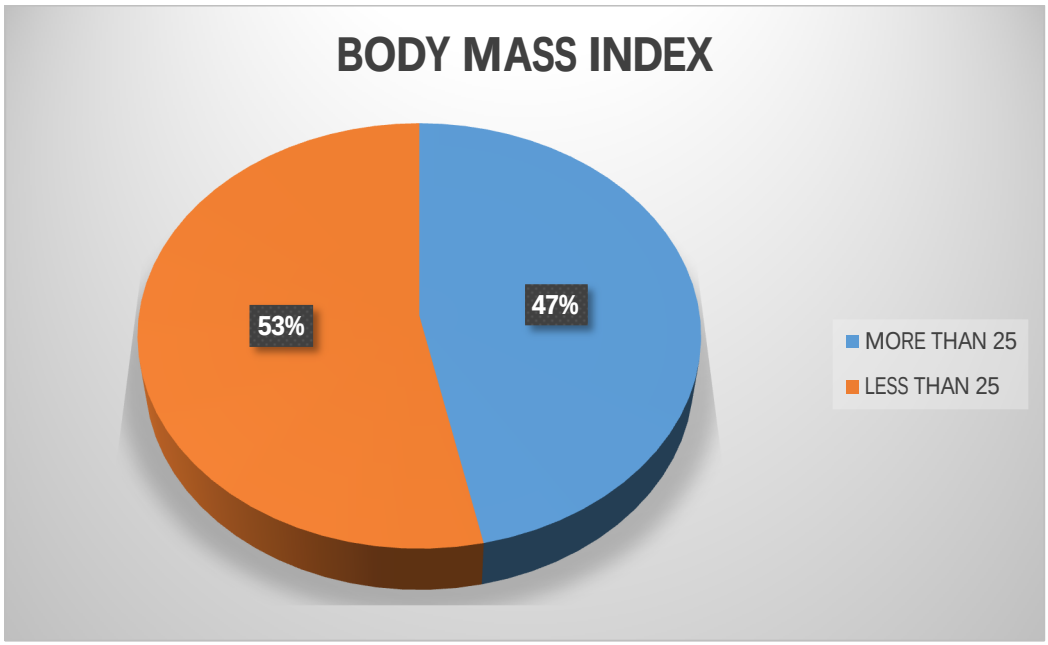


TABLE 9: BMI DISTRIBUTION IN NAFLD

USG GRADING	BMI (Kg/m^2)	
	>25	<25
GRADE I	4	16
GRADE II	12	14
GRADE III	12	2
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

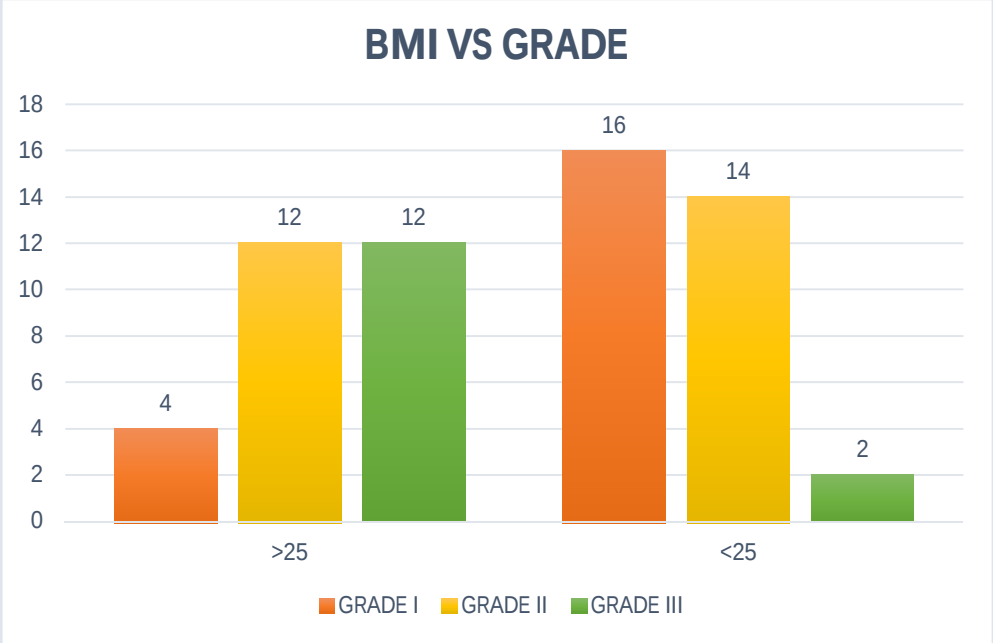


TABLE 10 : SGOT LEVEL IN THE PATIENTS

SGOT (U/L)	NO OF PATIENTS	PERCENTAGE
>35	16	27%
<35	44	73%

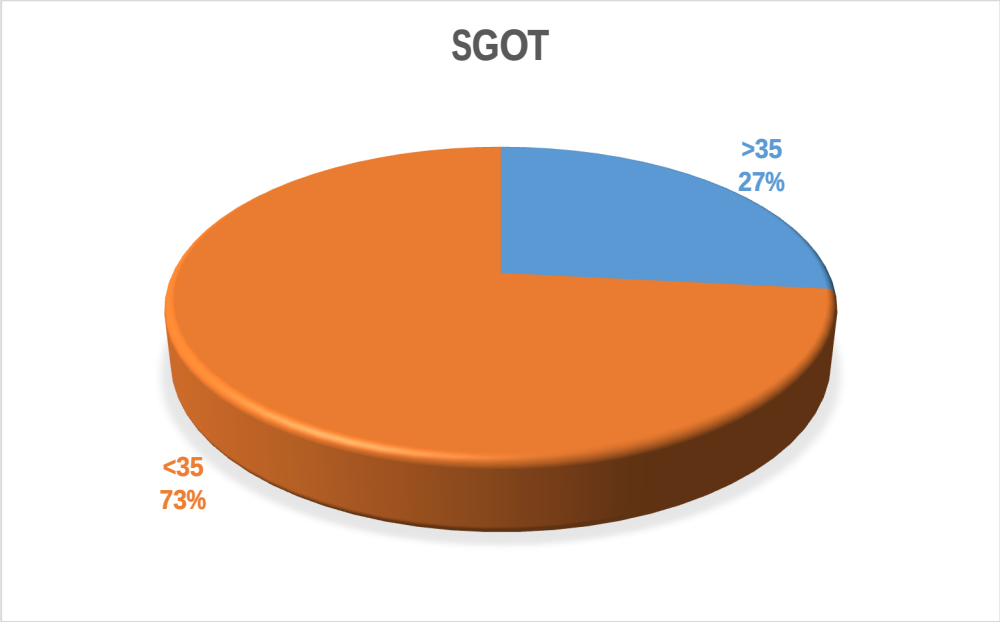


TABLE 11 : COMPARISON OF SGOT WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	SGOT (U/L)	
	>35	<35
GRADE I	0	20
GRADE II	5	21
GRADE III	11	3
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

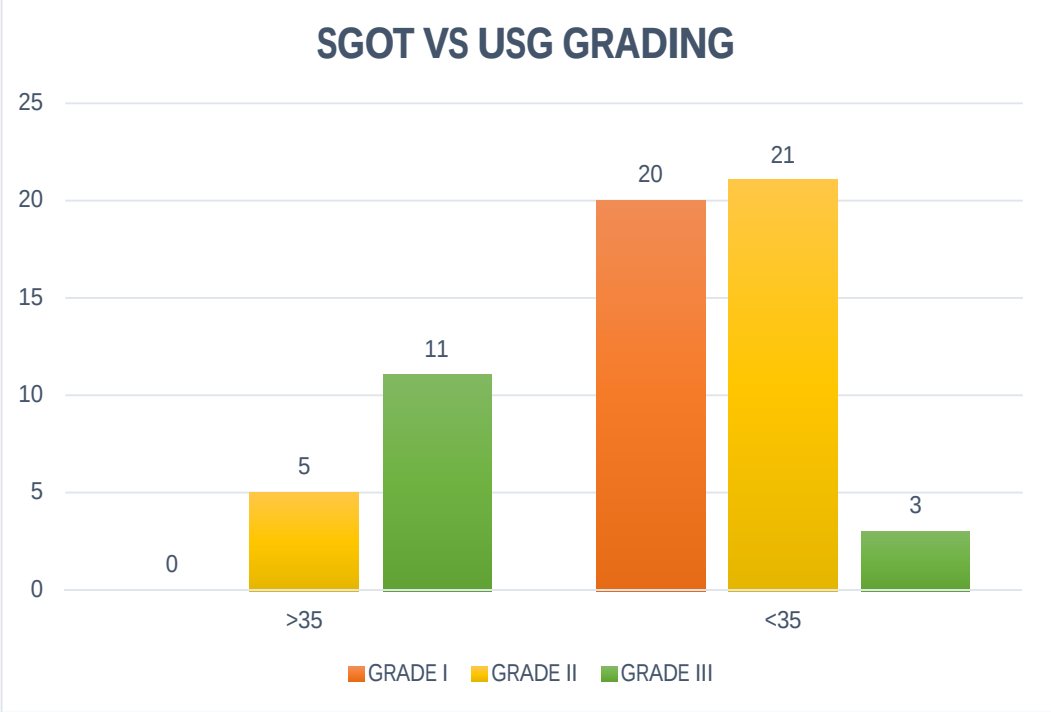


TABLE 12 : SGOT LEVEL IN THE PATIENTS

SGPT (U/L)	NO OF PATIENTS	PERCENTAGE
>35	17	28%
<35	43	72%

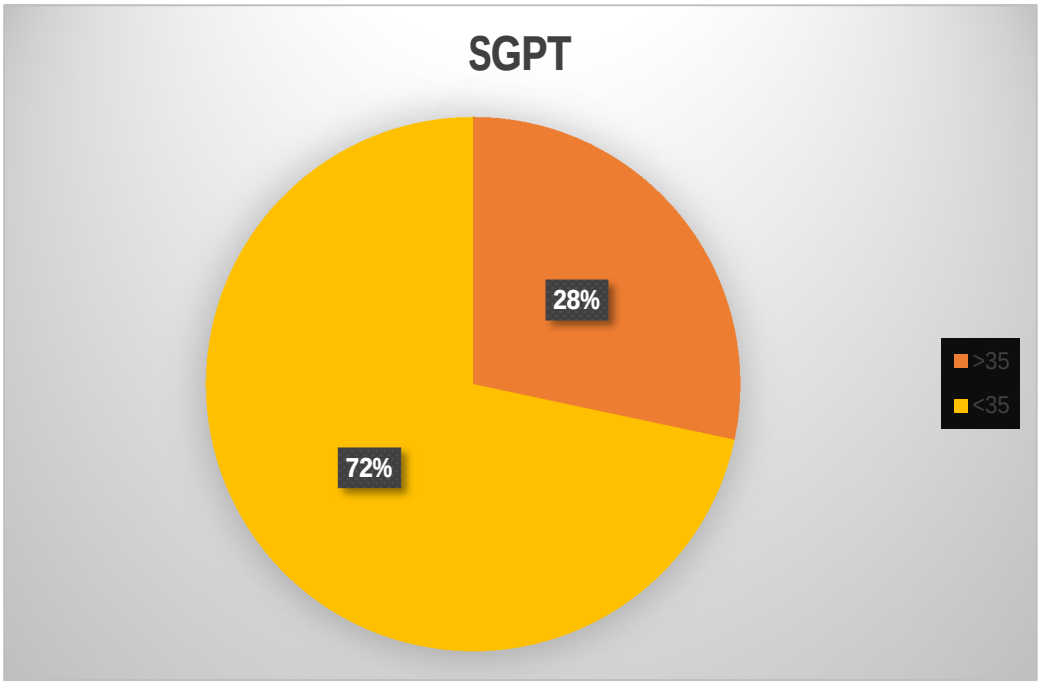


TABLE 13 : COMPARISON OF SGOT WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	SGPT (U/L)	
	>35	**<35**
GRADE I	1	19
GRADE II	5	21
GRADE III	11	3
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

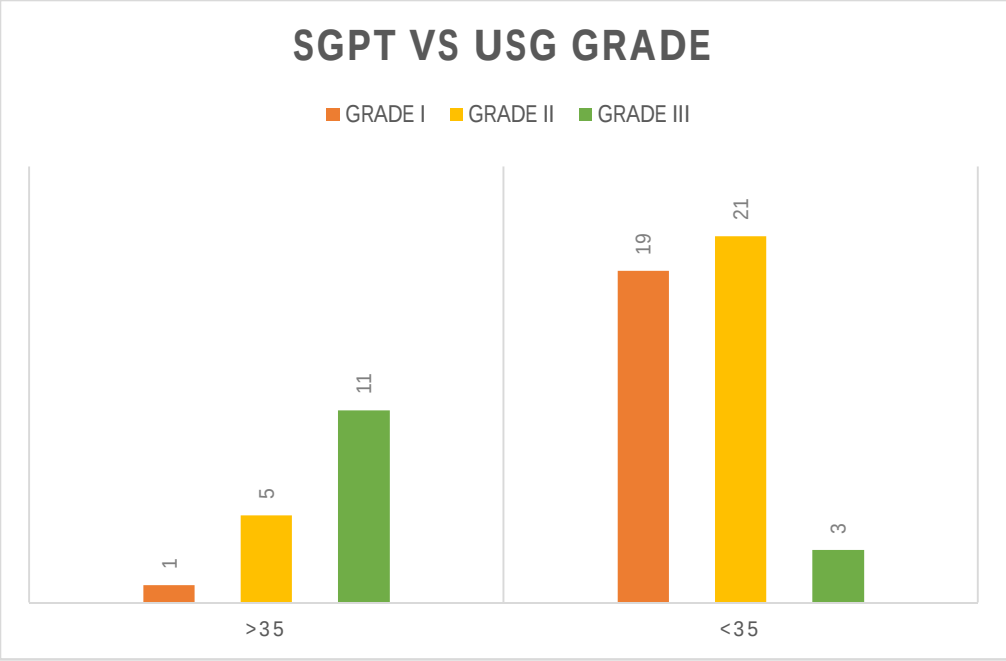


TABLE 14 : ALP LEVEL IN THE PATIENTS

ALP (U/L)	NO OF PATIENTS	PERCENTAGE
>150	12	20%
<150	48	80%

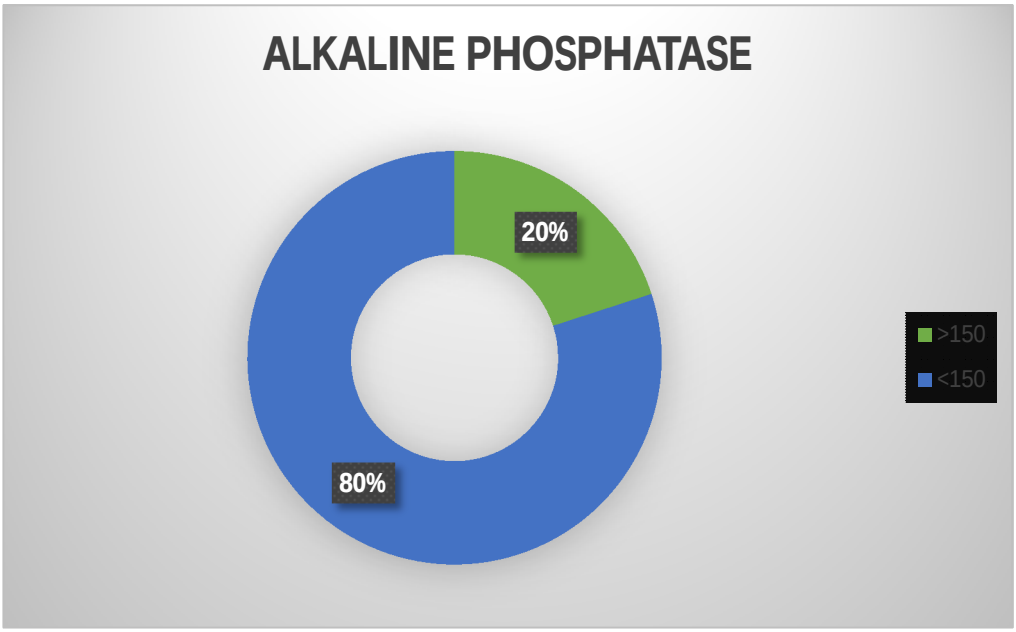


TABLE 15 : COMPARISON OF ALP WITH GRADING OF FATTY LIVER IN NAFLD

USG GRADING	ALKALINE PHOSPHATASE (U/L)	
	>150	**<150**
GRADE I	0	20
GRADE II	4	22
GRADE III	8	6
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

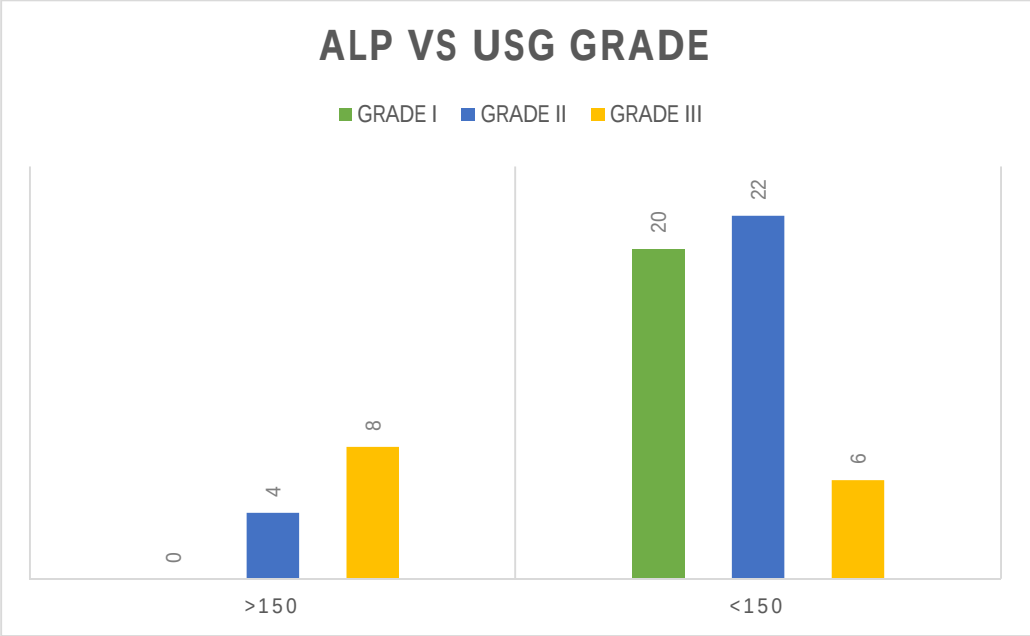


TABLE 16 : SERUM BILIRUBIN LEVEL IN THE PATIENTS

BILIRUBIN	NO OF PATIENTS	PERCENTAGE
ABNORMAL	2	3%
NORMAL	58	97%

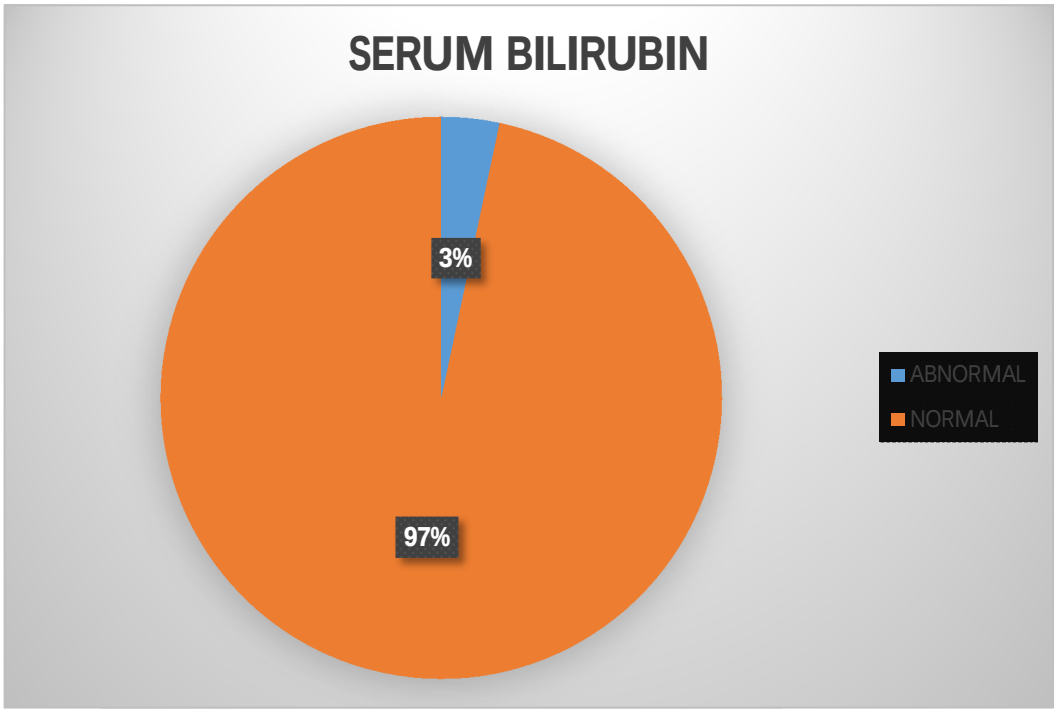


TABLE 17 :COMPARISON OF BILIRUBIN WITH GRADING OF FATTY LIVER IN NAFLD

USG GRADING	BILIRUBIN (mg/dl)	
	ABNORMAL	NORMAL
GRADE I	0	20
GRADE II	0	26
GRADE III	2	12
KRUSKAL WALLIS TEST		
P VALUE - 0.033		
SIGNIFICANT		

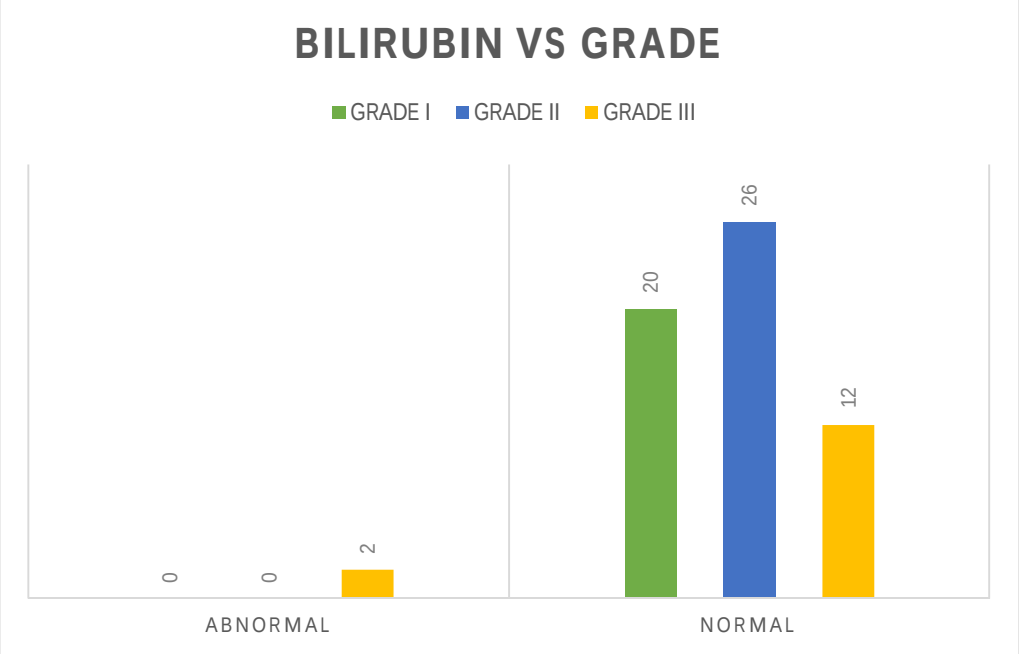


TABLE 18 : SERUM PROTEIN LEVEL IN THE PATIENTS

SERUM PROTEIN	NO OF PATIENTS	PERCENTAGE
ABNORMAL	2	3%
NORMAL	58	97%

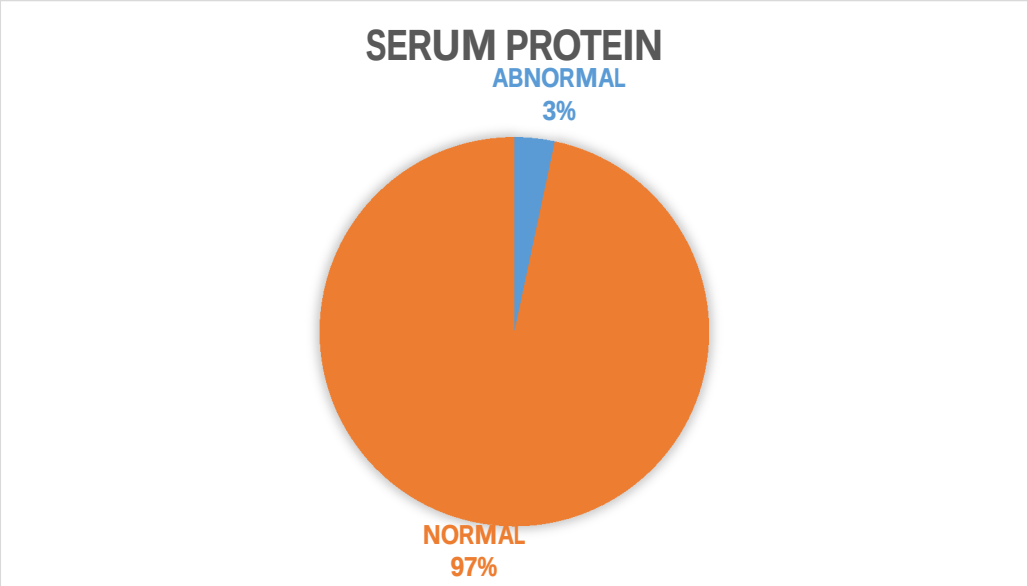


TABLE 19 : COMPARISON OF SERUM PROTEIN WITH GRADING OF FATTY LIVER IN NAFLD

USG GRADING	SERUM PROTEIN	
	ABNORMAL	NORMAL
GRADE I	0	20
GRADE II	0	26
GRADE III	2	12
KRUSKAL WALLIS TEST		
P VALUE - 0.033		
SIGNIFICANT		

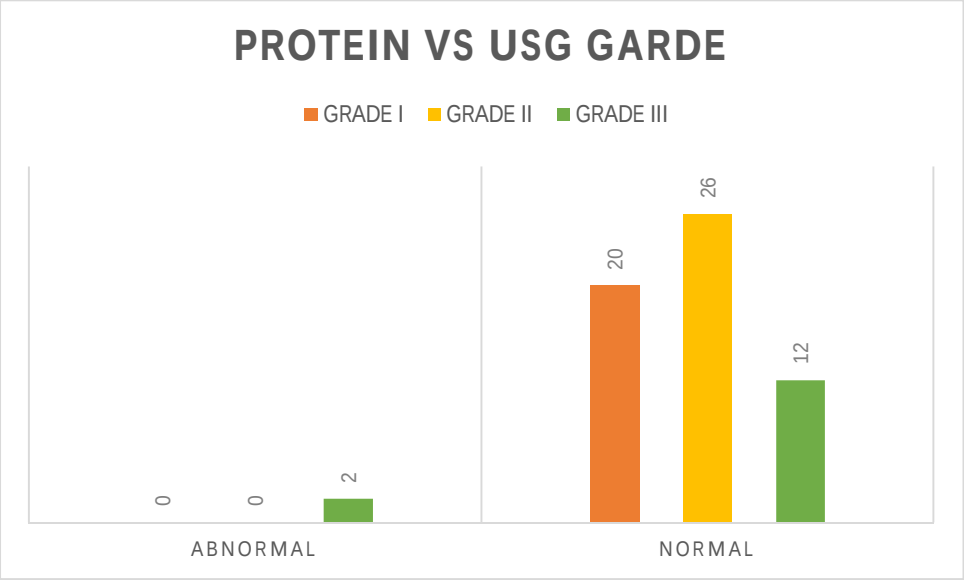


TABLE 20 : PLATELET LEVEL IN THE PATIENTS

PLATELET COUNT	NO OF PATIENTS	PERCENTAGE
ABNORMAL	2	3%
NORMAL	58	97%

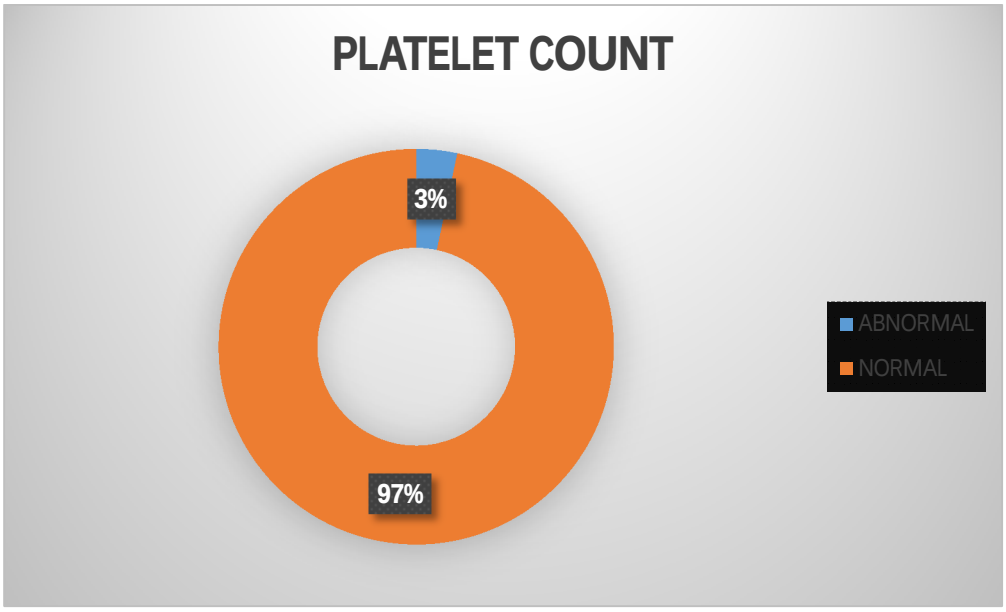


TABLE 21 : COMPARISON OF PLATELET COUNT WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	PLATELET COUNT	
	ABNORMAL	NORMAL
GRADE I	0	20
GRADE II	0	26
GRADE III	2	12
KRUSKAL WALLIS TEST		
P VALUE - 0.033		
SIGNIFICANT		

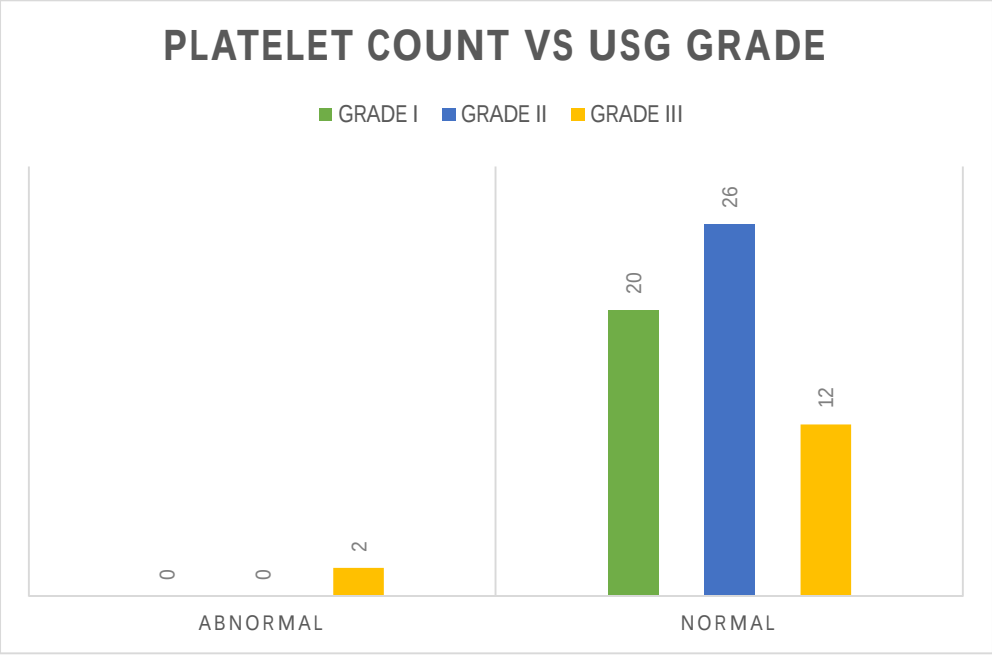


TABLE 22 : COMPARISON OF FASTING BLOOD SUGAR WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	FASTING BLOOD SUGAR (mg%)	
	MEAN	SD
GRADE I	127.7	8.87
GRADE II	137.12	16.01
GRADE III	158.01	21.8
ANOVA		
P VALUE - 0.001		
SIGNIFICANT		

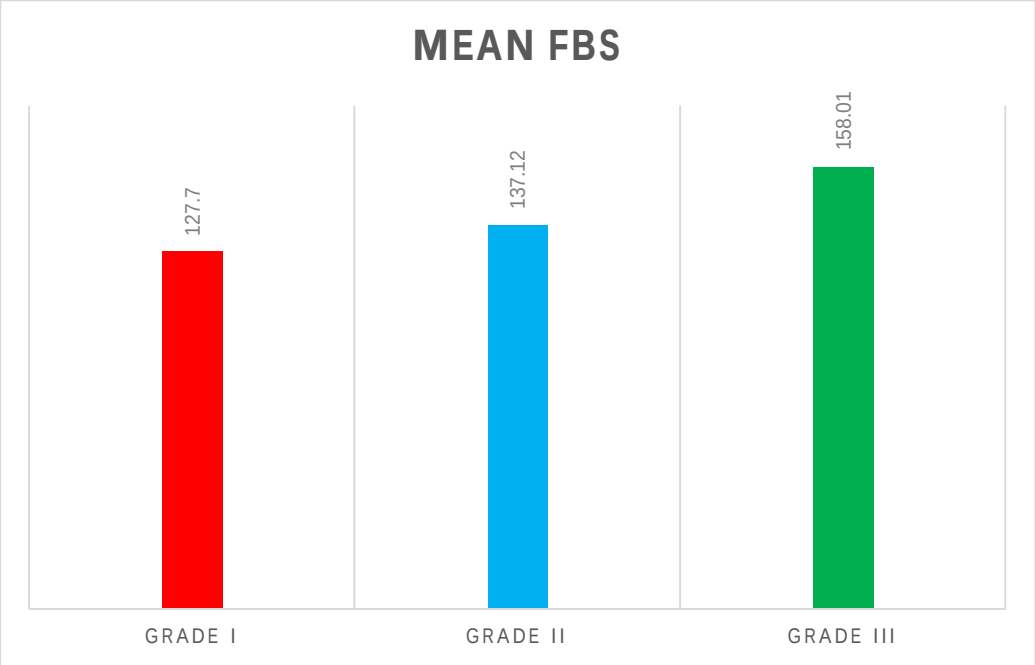


TABLE 23 : COMPARISON OF POST PRANDIAL BLOOD SUGAR WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	POST PRANDIAL BLOOD SUGAR (mg%)	
	MEAN	SD
GRADE I	151.05	12.02
GRADE II	168.5	26.18
GRADE III	198.86	52.08
ANOVA		
P VALUE - 0.001		
SIGNIFICANT		

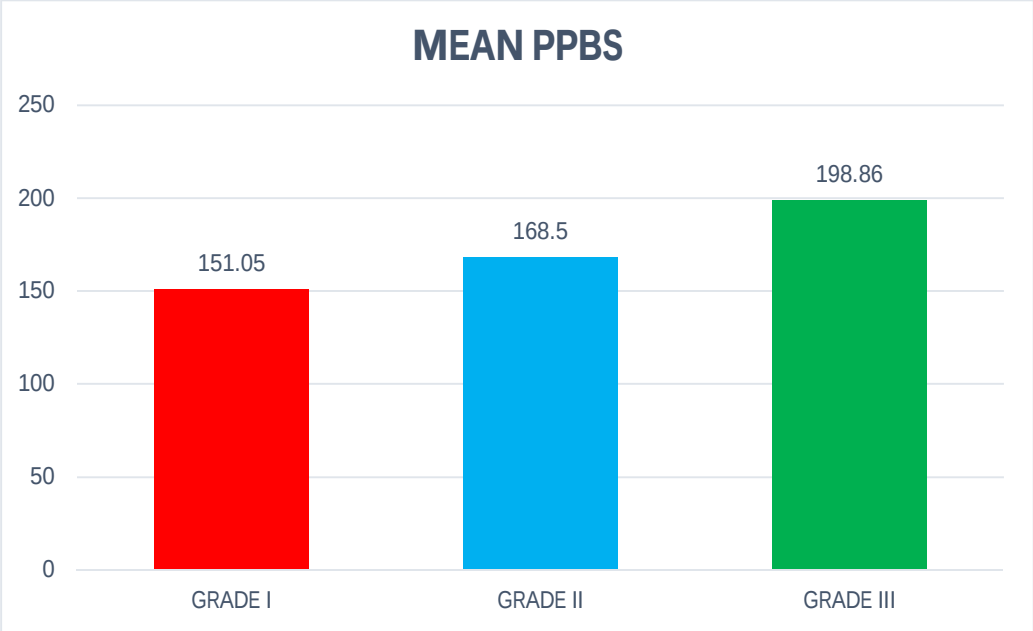


TABLE 24 : COMPARISON OF HBA1C WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	HBA1C (%)	
	MEAN	SD
GRADE I	6.08	0.68
GRADE II	6.73	0.78
GRADE III	8.36	0.92
ANOVA		
P VALUE - 0.001		
SIGNIFICANT		

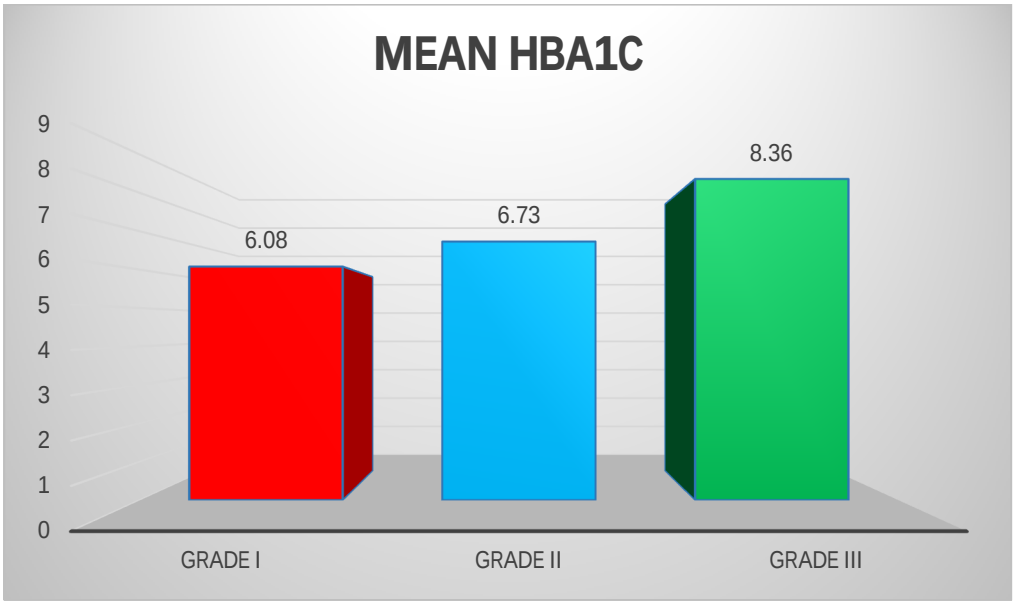


TABLE 25 : COMPARISON OF DURATION OF DISEASE WITH GRADES OF FATTY LIVER IN NAFLD

USG GRADING	DISEASE DURATION IN YEARS	
	MEAN	SD
GRADE I	5.75	1.07
GRADE II	6.54	1.63
GRADE III	6.64	2.02
ANOVA		
P VALUE - 0.167		
NON SIGNIFICANT		

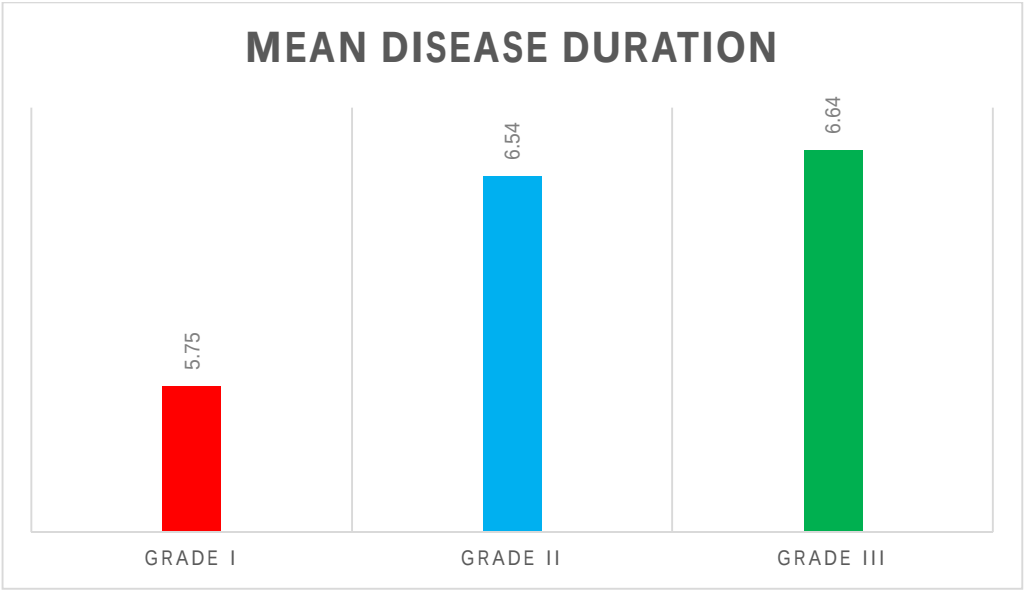


TABLE 26 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH FATTY LIVER IN NAFLD

USG GRADING	Kpa	
	MEAN	SD
GRADE I	5.42	1.17
GRADE II	7.11	1.89
GRADE III	12.22	1.34
ANOVA		
P VALUE - 0.001		
SIGNIFICANT		

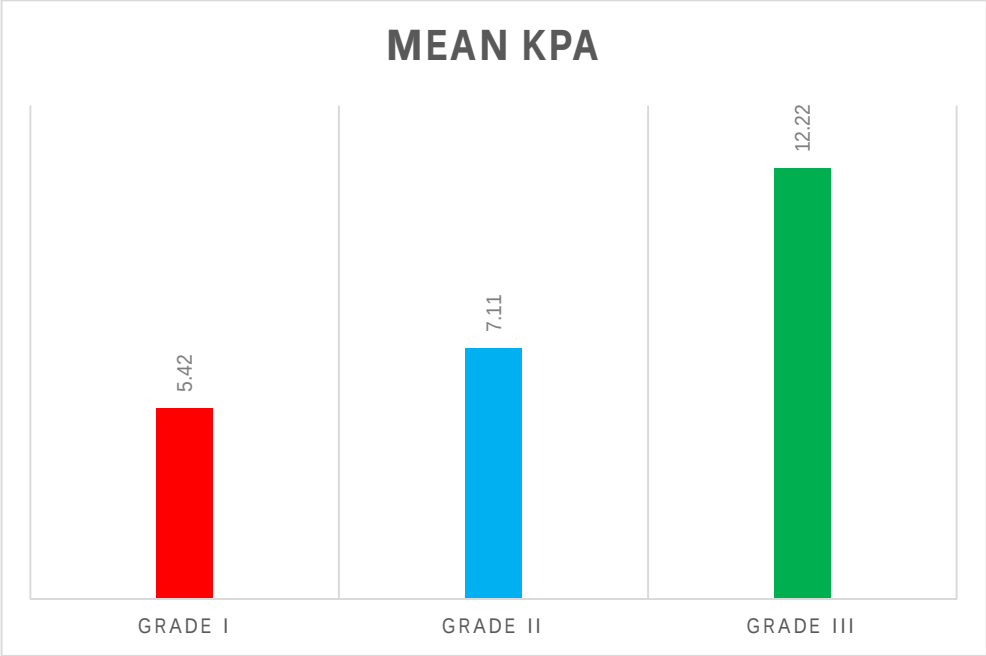


TABLE 27 :COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH AGE OF PATIENTS

Kpa	AGE IN YEARS	
	MEAN	SD
<6	54.04	5.89
>6	58	5.07
UNPAIRED T TEST		
P VALUE - 0.007		
SIGNIFICANT		

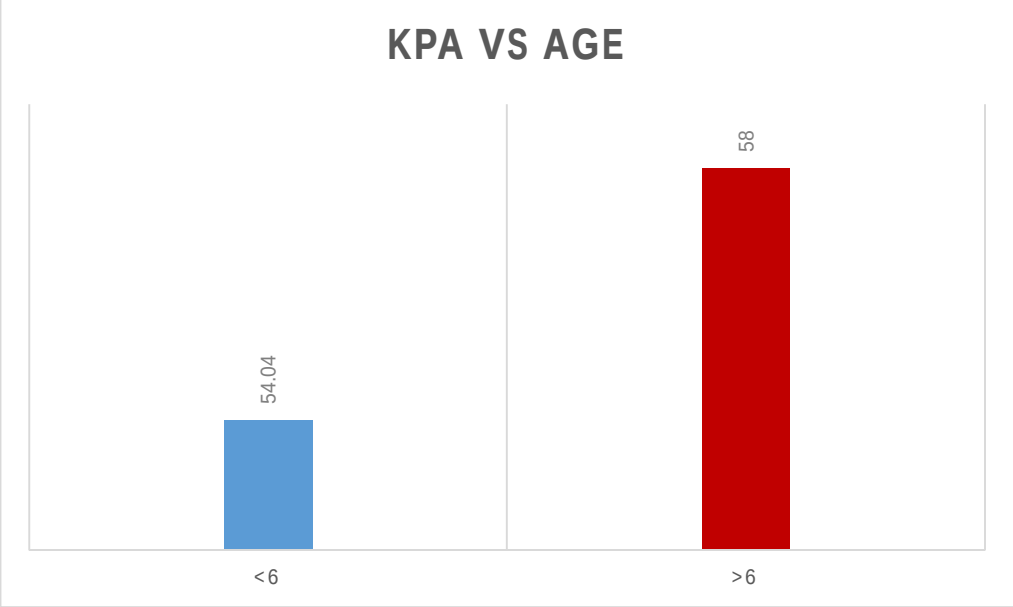


TABLE 28 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH FBS OF PATIENTS

kPa	FASTING BLOOD SUGAR (mg%)	
	MEAN	SD
<6	128.69	9.31
>6	146.62	21.23
UNPAIRED T TEST		
P VALUE - 0.001		
SIGNIFICANT		

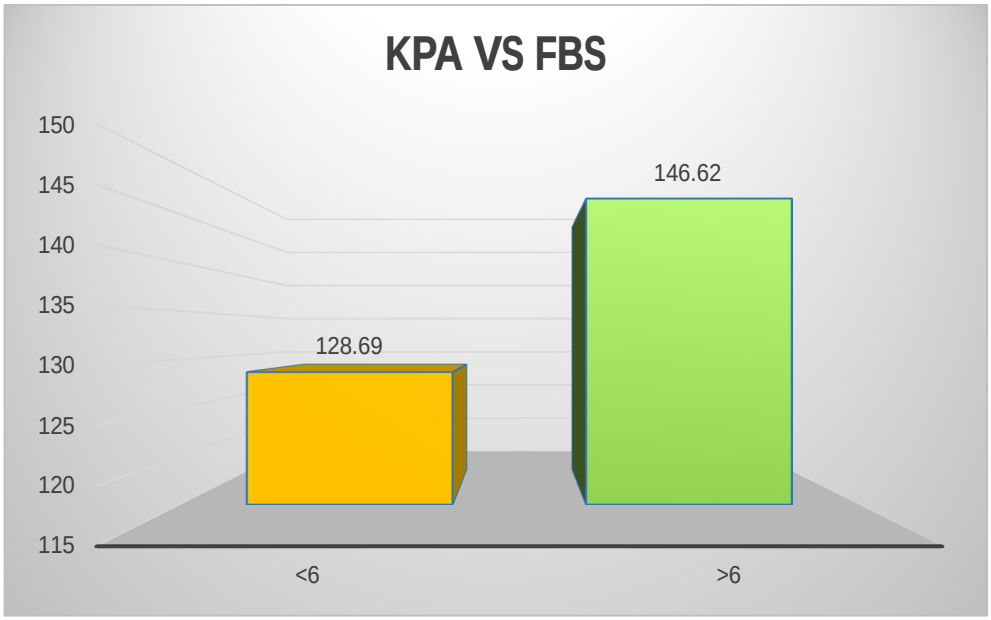


TABLE 29 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH PPBS OF PATIENTS

kPa	POSTPRANDIAL BLOOD SUGAR (mg%)	
	MEAN	SD
<6	153.15	13.11
>6	182.47	41.59
UNPAIRED T TEST		
P VALUE - 0.001		
SIGNIFICANT		

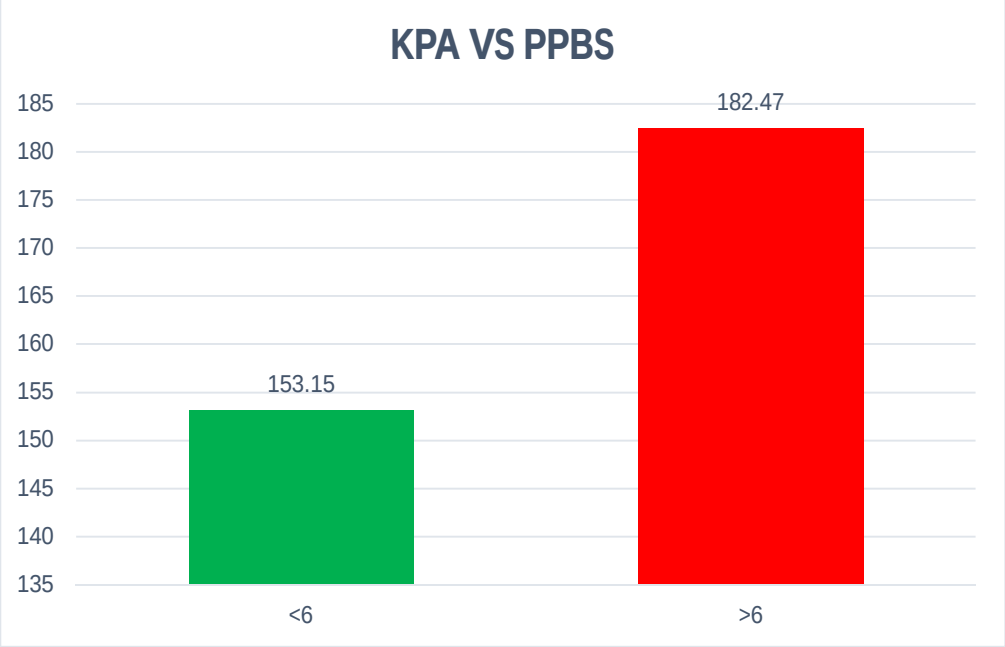


TABLE 30 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH HBA1C OF PATIENTS

kPa	HBA1C (%)	
	MEAN	SD
<6	6.11	0.64
>6	7.49	1.12
UNPAIRED T TEST		
P VALUE - 0.001		
SIGNIFICANT		

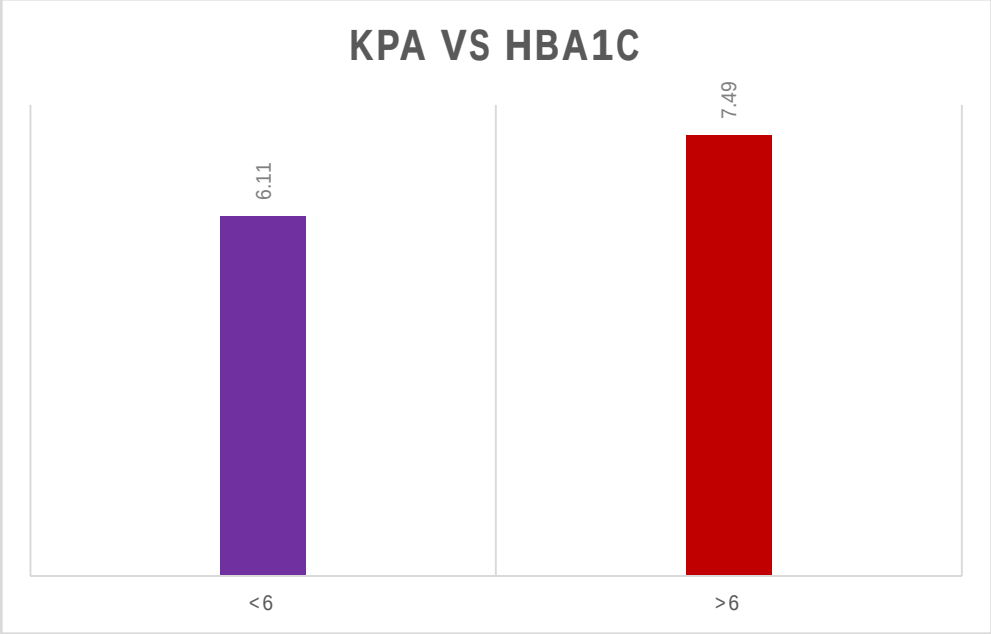


TABLE 31 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH DURATION OF DIABETES

Kpa	DURATION OF DISEASE IN YEARS	
	MEAN	**SD**
<6	5.65	0.97
>6	6.79	1.8
UNPAIRED T TEST		
P VALUE - 0.005		
SIGNIFICANT		

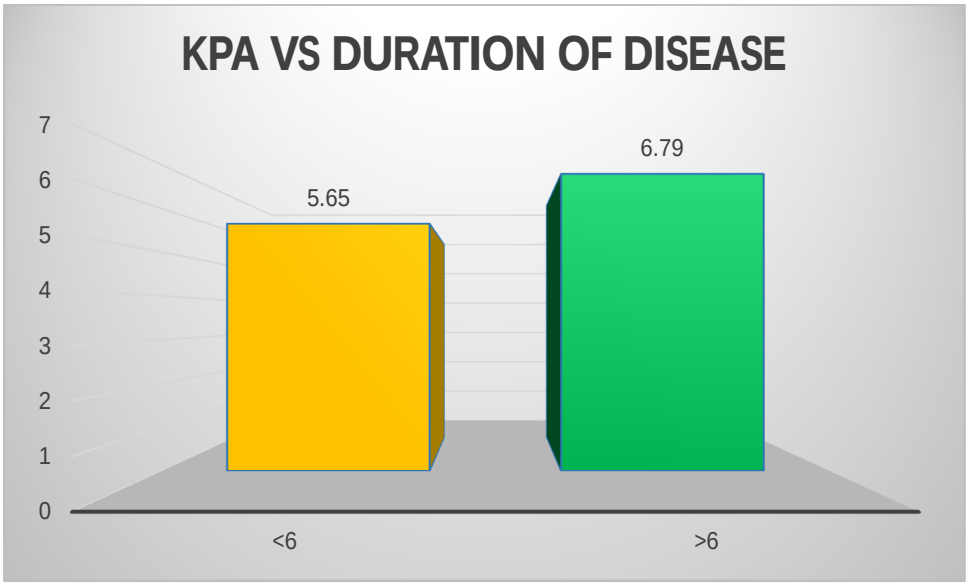
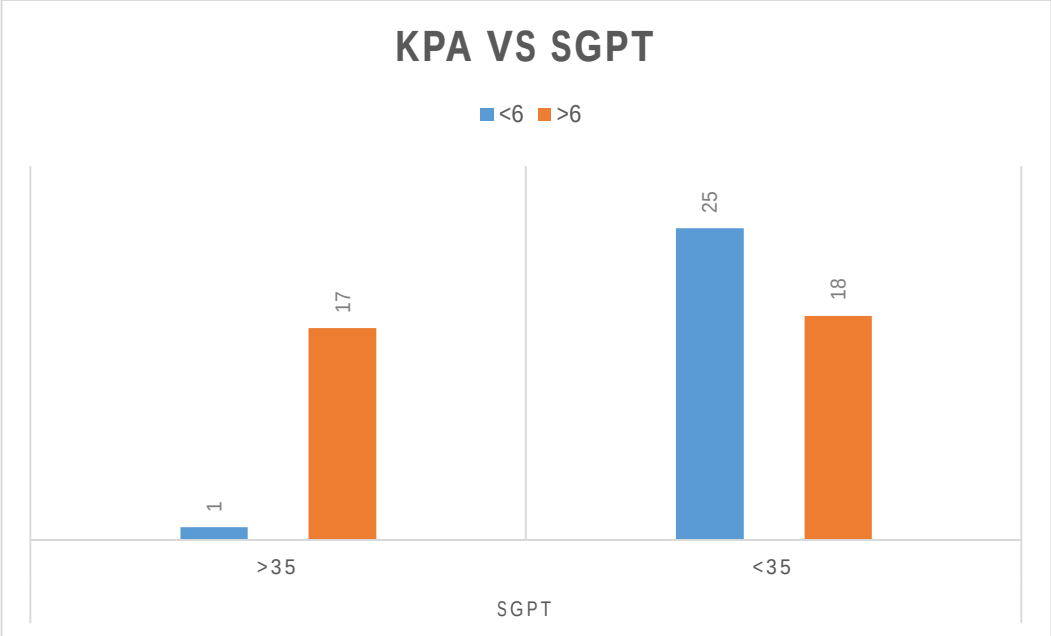


TABLE 32 : COMPARISON OF Kpa LEVEL OF FIBROSCAN WITH SGPT OF PATIENTS

Kpa	SGPT (U/L)	
	>35	**<35**
<6	1	25
>6	17	18
CHI SQUARE TEST		
P VALUE - 0.001		
SIGNIFICANT		



DISCUSSION

DISTRIBUTION OF SEVERITY OF FATTY LIVER ON USG:

In this study, 33% of patients had grade I, 43% had grade II and 24% had grade III fatty liver. A study conducted by Roli Agarval et al showed that 48.1%, 40.3%, 11.3% had grade I, II, III fatty liver respectively which was comparable to the observations made in this study.

COMPARING MEAN AGE GROUP WITH USG:

Of 60 patients, 12 patients are of age group <50 years, 36 patients are between 51-60 years and 12 patients belongs to age group >60 years.

Mean age of patients who had grade I, grade II, grade III fatty liver was 54.2 years, 57.65 years, 56.71 years respectively. No statistically significant relationship was found between age and ultrasound grading of fatty liver.

USG GRADING AND SEX:

In this study, 43% are male and 57% are female. Females are majority in this study. In an Indian study by D Amarapurkar et al in which there was female predominance of 52.2%. In this study female patients are high in number in grade I, II, III fatty liver. But it is not statistically significant.

USG GRADING AND BMI:

BMI was > 25 kg/m^2 in 28 patients other patients had BMI < 25kg/m^2.

In the study done by Daad H Akbhar et al, obesity was identified as an independent factor for development of NAFLD. [57]

Out of 28 patients with BMI > 25 kg/m^2 , 4 patients had grade I , 12 had grade II and 12 had grade III fatty liver which are statistically significant.

LIVER FUNCTION TEST:

In this study, 27% (16 patients) had SGOT >35 U/L . Of these 16 patients, 5 patients had grade II and 11 patients had grade III fatty liver.

28% (17 patients) had SGPT >35 U/L and 1 patient, 5 patients, 11 patients had fatty liver of grade I, II, III respectively.

20% (12 patients) had ALP >150 U/L , of these 4 had grade II and 12 had grade III fatty liver.

All three are statistically significant.

Only 2 patients had abnormal serum bilirubin and serum protein level. Other 58 patients had normal values.

Roli Agarwal et al reports elevated SGOT and SGPT in 97.6% and 98.4% respectively. Mofrad et al [58] studied NAFLD in 2 groups. Of which

one group comprises of 50 cases showed normal SGPT values and second group comprises of 50 cases with elevated SGPT values.

COMPARING FBS, PPBS, HbA1c WITH USG:

Patients with grade I fatty liver had mean FBS of 127.7 mg%, grade II had mean FBS of 137.12 mg% and grade III had mean FBS of 158.01 mg%.

Mean PPBS was 151.08 mg%, 168.5 mg%, 198.86 mg% in grade I, II, III fatty liver.

Mean HbA1c was 6.08% , 6.73%, 8.36% in grade I , II and III fatty liver group respectively.

All 3 i.e.,FBS, PPBS, HbA1c with USG are statistically significant.

COMPARING Kpa OF FIBROSCAN WITH USG:

In this study the mean Kpa value for the patients with grade I fatty liver was 5.42, grade II was 7.11, grade III was 12.22.

COMPARING Kpa OF FIBROSCAN WITH FBS, PPBS, HbA1c:

In this study patient with Kpa <6 had mean FBS, PPBS, HbA1c of 128.69 mg%, 153.15 mg%, 6.11 % respectively.

COMPARING Kpa VALUE OF FIBROSCAN WITH SGPT:

Of 60 patients, 17 patients who had SGPT >35 U/L had Kpa value >6 which is statistically significant.

LIVER STIFFNESS ASSEESSMENT:

Of 60 patients, 32 patients has Kpa value <6, 14 patients has Kpa value between 6 – 8 , 18 patients has Kpa between 8 – 12.5 Kpa (F3 fibrosis), 6 patients has Kpa values >12.5 (F4 fibrosis).

The patients who has grade I, Grade II, Grade III fatty liver has mean Kpa values of 5.42, 7.11, 12.22 .

LIMITATION:

1. Small study group since fibroscan cannot be done in more number of patients.
2. Selection bias towards the patients.
3. Lack of histological confirmation since liver biopsy remains gold standard.
4. Blood test like AST may fluctuate and may increase in non liver related problems like muscle injury.

CONCLUSION

1. Patients with diabetes has higher prevalence of NAFLD than patient with non diabetes.

2. In this study, females sex group has higher prevalence of occurance of Non alcoholic fatty liver disease. (57%) and the common age group was 51 – 60 years.

3. There was significant relation observed between Body mass index, Fasting blood sugar, Post prandial blood sugar, HbA1c, SGPT, SGOT and the prevalence of fatty liver by USG. Diabetic control correlates well with the study. Uncontrolled diabetic have high grade of fibrosis.

4. 3 patients with grade 2 fatty liver has Kpa value of more than >12. Hence fibroscan helps in early diagnosis of fibrosis.

5. There was no significant relation observed between age, duration of disease with NAFLD.

6. Out of 60 patients only 2 patients has abnormal serum bilirubin, serum protein and platelet values.

BIBLIOGRAPHY

1. Schaffner F, Thaler H, Non alcoholic fatty liver disease . Prog liver disease1986;8:283-98.

2. Prevalence of Fatty Liver Disease among Type 2 DiabetesMellitus Patients and its Relation to Insulin Resistance,S Merat et al, Middle East Journal of Digestive Diseases/ Vol.1/ No.2/ September 2009.

3. Ludwig Y, Viggiano TR, McGill DB, ctt BJ, Nonalcoholic steatohepatitis: Mayo Clin Proc 1980, 55:434-438.

4. Marchesini G, Brizi M, Morselle labate AM, et al NAFLD and insulin resistance: Am J Med 1999: 107:450-5.

5. Guidorizzi de siqueira AC, Cotrim, Rocha, et al NAFLD and insulin resistance. Eur J gastroenterol hepatol 2005:17:837-41.

6. Chitturi S, Abeygunasekara S, Farrell GC, et al. NASH and insulin resistance. Hepatology 2002, 35:373-9.

7. Silverman JF, Pories WJ, Caro JF. Liver pathology in diabetes mellitus and morbid obesity. Pathol Annu 1989, 24:275-302.

8. Zelman.S. The liver in obesity. Arch. Internal Medicine 1952; 90:141-156 Overview: an introduction to NASH and related fatty liver disordersGeoffrey C. Farrell, et al, book- First published 2005.

9. Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Tani S, Goto M. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988;27:142-9.

10. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in northern Italy. Ann Intern Med 2000;132:112-7.

11. Luyckx FH, Desaive C, Thiry A, et al. Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. Int J Obes Relat Metab Disord 1998;22:222-6.

12. Chitturi S, Farrell GC, George J. Non-alcoholic steatohepatitis in the Asia-Pacific region: future shock? J Gastroenterol Hepatol 2004; 19 : 368-74.

13. Mohan V, Farooq S, Deepa M et al. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation todifferent grades of glucose intolerance and metabolic syndrome. Diabetes Res ClinPract. 2009;84:84-91

14. Struben VM, Hespenheide EE, Caldwell SH. NASH and cryptogenic cirrhosis within kindreds. Am.J. Med 2000;108: 9-13

15. Willner IR, Waters B, Patil SR et al. Ninety patients with NASH: insulin resistance, familial tendency, and severity of disease. Am.J.gastroenterol.2001;96:2957-61

16. Adelmalek MF, Liu C, Shuster J et al. familial aggregation of insulin resistance in first degree relatives of patient with NAFLD.Clin. gastroenterol.hepatol.2006;4:1162-69.

17. Peterson KF, Dufour S, Befroy et al. Impaired mitochondrial activity in the insulin-resistant offspring of diabetes with type 2 diabetes with type 2 diabetes.N.Engl.J.Med 2004;350;664-671.

18. GI Epidemiology: nonalcoholic fatty liver disease,P. ANGULO, Aliment PharmacolTher 25, 883–889.

19. Day CP. Pathogenesis of steatohepatitis. Balliere's Best Pract Res ClinGastroenterol2002; 16: 663–78

20. Lemasters JJ Dying a thousand deaths: Redundant pathways from different organelles to apoptosis and necrosis.Gatroenterology 2005;129:351-360

21. Amidi F, French BA , Chung D et al.M-30 and 4HNE are sequestered in different aggresomes.Exp .Mol.path 2007;83:296-300

22. Su Q,Tsai J,XU E et al. Apolipoprotein B100 acts as a molecular link between lipid induced endoplasmic reticulum stress and hepatic insulin resistance. Hepatology 2009;50:77-84

23. Friedman SL. Hepatic stellate cells: Protean, multifunctional, and enigmatic cells of the liver.Physiol.rev.2008;88:125-172

24. Simple Noninvasive Systems Predict Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease,Paul Angulo, Elisabetta Bugianesi, Einar S. Bjornsson, Phunchai.

25. GI Epidemiology: nonalcoholic fatty liver disease,P. ANGULO, Aliment PharmacolTher 25, 883–889.

26. Matteoni CA, Younossi ZM, Gramlich T et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116:1413–9.

27. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of NASH syndromes. Semin Liver Dis 2001; 21:17-26.

28. Paggioni R, Fantuzzi G, Gabay C et al, Leptin deficiency enhances sensitivity to endotoxin-induced lethality. Am J Physiol 1999;276:R136 R142.

29. Rashid M, Roberts EA. NASH in children. J Pediatr Gastroenterol Nutr 2000;30:48-53.

30. Leonarduzzi G, Scavazza, A, Biasi F, et al. The Lipid peroxidation end product $-hydroxy-2,3-noneal up-regulates TGF β1 expression in the macrophage lineage: a link between oxidative injury and fibrosclerosis. FASEB J 1997;11:851-857.

31. Curzio M, Esterbauer H, Dianzani MU. Chemotactic activity of hydroxyalkenals on rat neutrophils. Int J Tissue React 1985;7:147-142.

32. Manton ND, Lipsett J, Moore DJ, Davidson GP< Bourne AJ, Couper RTI, NASH in children and adolescents. Med J Aust 2000;173:476-479.

33. Caldweel SH, Oelsner DH, lezzoni JC, Hespenheide EE, Battle EH,Driscoll CJ. Crptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999;29:664-669.

34. Angul P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with NASH. Hepatology 1999;30:1356-1362.

35. Bacon BR< Farahvash MJ, Janney CG, Neuschwander-Tetri BA> NASH: an expanded clinical entity. Gastroenterology.1994;107:1103 1109.

36. Pantsari MW, Harrison SA. Nonalcoholic fatty liver disease presenting with an isolated elevated alkaline phosphatase. J ClinGastroenterol. 2006;40:633–635.

37. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis:accuracy of UG for detection-analysis 300 cases.Radiology 2003;227:89-94

38. Abate N, Burns D, Peshock RM, Garg A, Grandy SM. Estimation of adipose tissue mass by MRI: validation against dissection in human cadavers. Lipid Res 1994;35:1490-6

39. Leen E, Goldberg JA, Angerson WJ, McArdle CS. Potential role of Doppler perfusion index in selection of patients with colorectal cancer for adjuvant chemotherapy. Lancet. 2000; 355:34–37.

40. Jacobs JE, Birnbaun BA, Shapiro MA, et al. Diagnostic criteria for fatty infiltration of the liver on contrast-enhanced helical CT. AJR Am J Reontgenol 1998;171;659-64

41. 41.Alpren MB, Lawson TL, Foley DW, et al. Focal hepatic masses and fatty infiltration detected by enhanced dynamic CT. Radiology 1986;158:45-9

42. 42.Schlemmer H-P, Sawatzki T, Sammet S et al. Hepatic phospholipids in alcoholic liver disease assessed by proton decoupled 31P MR spectroscopy. J Hepatol 2005;42:752-9.

43. 43.Hall P de la M, Kirsch R (2005) patology of steatosis, NASH and related condition.In:Farrell GC, George J, Hall Pde la M et al. Fatty liver disease.NASH and related disorders.Malden ,MA Blackwell publishing , pp13-22.

44. 44. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA,Bacon BR. Non alcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol. 1999;94:2467–2474.

45. 45. Liver stiffness: a novel parameter for the diagnosis of liver disease, Hepatic Medicine: Evidence and Research may 2010: 249–67.

NON INVASIVE ASSESSMENT OF FIBROSIS OF LIVER USING FIBROSCAN IN PATIENTS WITH DIABETES MELLITUS

THESIS PROFORMA

GUIDE: CANDIDATE:

GENERAL INFORMATION

Name :

Age/sex :

Hospital No :

Address : Phone:

Occupation :

Literacy :

Per capita income:

Religion : Hindu/Muslim/Christian/Others

Diet :Veg/Non Veg/Mixed

Present history

S.No	SYMPTOM	PRESENT	ABSENT	DURATION
1.	Abdominal pain			
2.	Abdominal distension			
3.	Dyspepsia			
4.	Jaundice			
5.	UGI bleed			
6.	Oedema legs			
7.	Complications of diabetes			

HISTORY	DURATION	DRUGS
DIABETES MELLITUS		
CAD		
HYPERTENSION		
DYSLIPIDEMIA		
CHRONIC LIVER DISEASE		
THYROID DISORDERS		
CHRONIC KIDNEY DISEASE		
MALIGNANCY		

Any other Drugs:

Parentral nutrition: YES/NO

H/O:

Jaundice :

Abdominal Surgery :

Blood Transfusion :

Starvation :

HBV :

HCV :

Family H/O:

Personal H/O :

Alcohol :

Smoking:

Any other substance Abuse:

IV Drug abuse:

GENERAL EXAMINATION:

B.P: P.R Ht: WT: BMI :

Anemia- Icterus- Clubbing- Cyanosis- Pedal edema-

CVS-

R.S-

Per Abdomen –

CNS-

INVESTIGATIONS:

Tc	
Hb	
Platelet	
Urea	
Creatinine	
FBS	
PPBS	
HBA1C	
LFT: 1.S.Bilirubin/direct bilirubin 2.SGOT/SGPT/ALP 3.Protein/Albumin	
HBsAg	
Anti HCV	
HIV	
PT/INR	
CHOL/TGL/LDL/HDL	
USG Abdomen	
Fibroscan	

DIAGNOSIS:

INVESTIGATOR:

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õò¶ :

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«è£¬õ Üó² ñ¼ˆ¶õ, è™ÖK ñ¼ˆ¶õñ¬ùJ™ ñ¼. ,uh.ee;j⁋d⁋ nj t⁋ î¬ô¬ñJ™ ï¬ìªðÁ‹ Þ‰î ÝŒM™ âù¶ º¿àì™ ñŸÁ‹ ÞóˆîŠ ðK«ê£î¬ù ªêŒ¶ ªè£œ÷ º¿ ñù¶ì¡ ê‹ñF,A«ø¡.â¡¬ùŠ ðŸPò Mõóƒè¬÷ ð£¶è£Š¹ì¡ Þ‰î ÝŒM™ ªõOJì Ý†«êð¬í Þ™¬ô â¡Á ªîKMˆ¶, ªè£œA«ø¡. ï£¡ â‰î «ïóˆF½‹ ÝŒM™ Þ¼‰¶ Mô,A, ªè£œÀ‹ àK¬ñ à‡´ â¡Á ÜP«õ¡.

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MASTER CHART

S.No	NAME	AGE/SEX	FBS	PPBS	HbA1c	YEARS	Kpa	TREATMENT	BMI	SGOT	SGPT	ALP	CHOLESTEROL	TGL	HDL	USG	BILIRUBIN	S.PROTEIN	PLATELETS
1	gopinath	70/m	144	176	7	7	5.8	insulin	<25	<35	<35	<150	<200	<150	HIGH(>40)	GR 1	NORMAL	NORMAL	NORMAL
2	jacob	50/m	123	147	6	5	4.6	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
3	pushpavalli	45/f	127	148	5.4	5	4.9	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
4	nallendren	62/m	131	161	6.2	8	6.1	insulin+OHA	<25	<35	<35	<150	<200	<150	LOW(<40)	GR 1	NORMAL	NORMAL	NORMAL
5	bhuvaneshwari	54/f	120	142	5.1	5	4.7	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
6	rajeshwari	61/f	150	190	7	8	7.7	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
7	sandhiya	53/f	138	164	6.7	5	6.8	insulin	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
8	maniyan	71/m	154	188	7.6	10	9	OHA	>25	>35	>35	<150	>200	>150	LOW	GR 2	NORMAL	NORMAL	NORMAL
9	prabavathy	62/f	141	177	6.6	7	6.1	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
10	padmavathy	66/f	123	146	5.6	5	4.4	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
11	chitra	55/f	133	171	6.2	5	6.1	OHA	>25	<35	<35	<150	<200	<150	LOW	GR 2	NORMAL	NORMAL	NORMAL
12	anandavel	60/f	141	169	5.9	6	5.8	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
13	rukmani	52/f	118	139	5	4	4.8	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
14	radhamani	60/f	161	121	8.5	6	14	OHA	>25	>35	>35	>150	<200	<150	LOW	GR 3	NORMAL	NORMAL	NORMAL
15	shanthi	49/f	118	156	5.8	5	5.8	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
16	deivanai	54/f	161	191	9	5	13.8	OHA	>25	<35	<35	>150	>200	>150	LOW	GR 3	2.1	<3.5	1.12 L
17	murugesan	54/m	138	155	6.8	6	8.1	insulin	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
18	vanitha	48/f	118	138	4.8	5	4.6	OHA	<25	<35	<35	<150	<200	<150	LOW	GR 1	NORMAL	NORMAL	NORMAL
19	rajendren	49/m	131	147	6.1	5	6.1	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
20	sundari	50/f	122	155	5.8	5	5.9	OHA	>25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
21	lakshmi	56/f	153	192	8.6	6	11.1	insulin	<25	<35	<35	<150	<200	<150	LOW	GR 3	NORMAL	NORMAL	NORMAL
22	siva kumar	58/m	130	145	5.8	6	5.9	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
23	krishnan	45/m	118	141	6	5	5.2	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
24	kumar	56/m	125	150	6.2	6	5.5	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
25	indira	66/f	124	144	6.4	8	8.5	insulin	>25	>35	>35	<150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
26	logeshwari	30/f	125	151	6.5	16	7.5	insulin	>25	<35	<35	<150	<200	<150	LOW	GR 2	NORMAL	NORMAL	NORMAL
27	geetha	64/f	186	232	9	10	12	insulin+OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
28	mohan	60/m	111	138	6	5	6.1	OHA	<25	<35	<35	<150	<200	<150	LOW	GR 2	NORMAL	NORMAL	NORMAL
29	palanivel	62/m	148	188	6.5	7	5.2	insulin	>25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
30	sadhasivam	65/m	108	130	5.6	5	8.8	OHA	>25	>35	>35	>150	>200	>150	LOW	GR 2	NORMAL	NORMAL	NORMAL
31	amsaveni	51/f	118	139	6.1	5	4.6	insulin	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL

32	kalidas	58/m	181	289	9.8	7	11.2	insulin+OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
33	kuppusamy	54/m	141	163	7	6	5.7	OHA	>25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
34	ananth	56/m	134	159	7	6	5.7	OHA	<25	<35	<35	<150	>200	>150	LOW	GR 2	NORMAL	NORMAL	NORMAL
35	ponnusamy	62/m	141	187	7.3	8	6.9	insulin+OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
36	malliga	57/f	188	259	9	9	10	OHA	<25	>35	>35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
37	banumathi	60/f	149	201	8.8	10	12.6	OHA	>25	>35	>35	<150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
38	chinnan	54/m	128	152	5.6	5	5.6	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
39	kannan	49/m	118	140	5.6	5	4.3	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
40	sakthivel	56/m	143	177	7.5	8	14	OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
41	malarkodi	56/f	131	163	6.1	6	5.6	insulin	<25	<35	<35	>150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
42	rajan	64/m	136	170	8.5	10	10.2	insulin	>25	>35	>35	<150	<200	<150	HIGH	GR 3	NORMAL	NORMAL	NORMAL
43	nallammal	53/f	151	189	7.8	5	8.8	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
44	savithri	59/f	144	180	7	10	9.5	insulin+OHA	<25	<35	<35	<150	>200	>150	LOW	GR 2	NORMAL	NORMAL	NORMAL
45	sankar	48/m	132	156	6.7	5	6.5	OHA	>25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
46	anuradha	50/f	144	171	7.1	5	4.9	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
47	natchammal	52/f	134	158	7	5	12	OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
48	perumal	60/m	138	161	6.7	7	8	insulin	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
49	subramani	58/m	133	151	6.5	6	6.6	insulin	<25	<35	<35	<150	<200	<150	LOW	GR 2	NORMAL	NORMAL	NORMAL
50	senthil	57/m	144	171	7.5	5	11.4	insulin	>25	>35	>35	<150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
51	latha	31/f	140	162	6.5	15	5.1	insulin	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
52	nirmala	55/f	128	149	6.4	5	5.4	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
53	saraswathy	57/f	150	191	7.3	7	6.1	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
54	srinivasan	50/m	142	171	7.1	5	10.5	OHA	>25	<35	<35	<150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
55	ramesh	55/m	149	181	7.8	5	13	OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
56	meenatchi	48/f	128	146	6	5	4.8	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
57	pushpavalli	55/f	131	151	6.1	6	4.9	insulin	<25	<35	>35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
58	arumugam	65/m	139	161	6.6	8	5.5	OHA	<25	<35	<35	<150	>200	>150	LOW	GR 2	NORMAL	NORMAL	NORMAL
59	chellammal	59/f	151	190	8	7	13.2	OHA	>25	>35	>35	>150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
60	mary	50/f	120	139	6	5	4.9	OHA	<25	<35	<35	<150	<200	<150	LOW	GR 1	NORMAL	NORMAL	NORMAL
61	mohammed	60/m	130	151	6.8	8	5.8	insulin	>25	<35	<35	<150	<200	<150	LOW	GR 1	NORMAL	NORMAL	NORMAL
62	duraisamy	58/m	140	174	7	6	5.2	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
63	malliga	55/f	128	146	6.2	6	5.4	OHA	<25	<35	<35	<150	>200	>150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
64	paapathy	60/f	125	146	6.4	7	9.9	insulin	>25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL

65	vishwanathan	60/m	162	212	9	8	10.2	OHA	>25	<35	<35	<150	>200	>150	HIGH	GR 2	NORMAL	NORMAL	NORMAL
66	selvi	56/f	212	321	10	5	11.4	insulin+OHA	<25	>35	>35	<150	>200	>150	LOW	GR 3	NORMAL	NORMAL	NORMAL
67	ravi	55/m	125	148	6.2	5	5.1	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
68	suresh	50/m	131	154	6.6	5	5.3	OHA	<25	<35	<35	<150	<200	<150	HIGH	GR 1	NORMAL	NORMAL	NORMAL
69	suganthi	52/f	161	209	8	6	14	OHA	>25	>35	>35	>150	>200	>150	LOW	GR 3	2.2	<3.5	1.23 L
70	vimala	59/f	132	151	7	7	6.6	insulin	>25	<35	<35	>150	<200	<150	LOW	GR 2	NORMAL	NORMAL	NORMAL